VOLUME 101 • JUNE 1958 • NUMBER 6

A.M.A. ARCHIVES OF

INTERNAL MEDICINE

INDEX NUMBER

Surgical Results in Coarctation of the Aorta, Aortic Stenosis, and Pulmonary Stenosis
Maurice Campbell

Functional Isosthenuria
Charles R. Kleeman, Morton H. Maxwell, and Steven Witlin

The Effects of Induced Hypocalcemia on Myocardial Irritability and Conductivity
Bernard Kabakow and Milton J. Brothers

Atypical Heat Stroke, with Hypernatremia, Acute Renal Failure, and Fulminating Potassium Intoxication
Charles R. Baxter and Paul E. Teschan

A Review of the Current Status of Nonoperative Cholecystoangiography
Edwin M. Cohn and David M. Sklaroff

Tuberculosis, a Disease of Old Age
Robert G. Bloch

Sarcoidosis
Richard H. Ferguson and Jaime Paris

Chlorpromazine Jaundice
William F. Gebhart, Ray A. Van Ommen, Lawrence J. McCormack, and Charles H. Brown

Psychometabolic Changes in Phenylketonuria Treated with Low-Phenylalanine Diet
Hans Meyer, Edwin T. Mertz, Harold E. Stadler, Henry Leland, and Joseph Calandro

Hypoxia of Abnormal Physiologic Origin as the Final Common Pathway in Gastroduodenal Ulcer Genesis
Eddy D. Palmer and Jacques L. Sherman Jr.

The Clinical Significance of Serum Cyanocobalamin (Vitamin B_{12}) in Liver Disease
M. Rachmilewitz, Y. Stein, J. Aronovitch, and N. Grossowicz

The Electrocardiogram in Myocardial Infarction
Morris M. Weiss and Morris M. Weiss Jr.

Corticotropin and Corticosteroid Therapy in Tuberculosis
Roger M. Des Prez and Avrum Organick

Idiopathic Hypoparathyroidism
William Saphir and Antonio Cahué

Pericardial Biopsy with Vim-Silverman Needle
L. M. Sanghvi and K. C. Samuel

Books

News and Comment

Complete Contents on First Inside Page

AMERICAN MEDICAL ASSOCIATION PUBLICATION

anginaphobia: *must he live in fear?*

For the angina patient, fear of attack often restricts even *normal* activity. With Peritrate, you can restore confidence and help the patient live more fully—within the limits of his disability.

Peritrate®

brand of pentaerythritol tetranitrate

WARNER-CHILCOTT

TABLE OF CONTENTS

VOLUME 101 JUNE 1958 NUMBER 6

EDITORIALS

PAGE

Surgical Results in Coarctation of the Aorta, Aortic Stenosis, and Pulmonary Stenosis
Maurice Campbell, O.B.E., D.M., F.R.C.P., London 1017

ORIGINAL ARTICLES

Functional Isosthenuria
Charles R. Kleeman, M.D.; Morton H. Maxwell, M.D., and Steven Witlin, M.D., Los Angeles 1023

The Effects of Induced Hypocalcemia on Myocardial Irritability and Conductivity
Bernard Kabakow, M.D., and Milton J. Brothers, M.D., New York 1029

Atypical Heat Stroke, with Hypernatremia, Acute Renal Failure, and Fulminating Potassium Intoxication
Capt. Charles R. Baxter (MC), and Major Paul E. Teschan (MC), U. S. Army 1040

A Review of the Current Status of Nonoperative Cholecystoangiography
Edwin M. Cohn, M.D., and David M. Sklaroff, M.D., Philadelphia 1051

Tuberculosis, a Disease of Old Age
Robert G. Bloch, M.D., New York 1057

Sarcoidosis
Major Richard H. Ferguson (MC), and Capt. Jaime Paris (MC), U. S. A. F. 1065

Chlorpromazine Jaundice
William F. Gebhart, M.D.; Ray A. Van Ommen, M.D.; Lawrence J. McCormack, M.D., and Charles H. Brown, M.D., Cleveland 1085

Psychometabolic Changes in Phenylketonuria Treated with Low-Phenylalanine Diet
Hans Meyer, M.D.; Edwin T. Mertz, Ph.D.; Harold E. Stadler, M.D.; Henry Leland, Ph.D., and Joseph Calandro, M.T., Butlerville, Ind. 1094

Hypoxia of Abnormal Physiologic Origin as the Final Common Pathway in Gastroduodenal Ulcer Genesis
Lieut. Col. Eddy D. Palmer (MC), and Lieut. Col. Jacques L. Sherman Jr. (MC), U. S. Army 1106

The Clinical Significance of Serum Cyanocobalamin (Vitamin B_{12}) in Liver Disease
M. Rachmilewitz, M.D.; Y. Stein, M.D.; J. Aronovitch, M.Sc., and N. Grossowicz, Ph.D., Jerusalem 1118

The Electrocardiogram in Myocardial Infarction
Morris M. Weiss, M.D., and Morris M. Weiss Jr., Louisville 1126

Corticotropin and Corticosteroid Therapy in Tuberculosis
Roger M. Des Prez, M.D., and Avrum Organick, M.D., Fort Defiance, Ariz. 1129

Idiopathic Hypoparathyroidism
William Saphir, M.D., and Antonio Cahué, M.D., Chicago 1143

Pericardial Biopsy with Vim-Silverman Needle
L. M. Sanghvi, M.R.C.P. (London), D.T.M.&H. (England), and K. C. Samuel, M.D., Jaipur, India 1147

TREATMENT IN INTERNAL MEDICINE

The Treatment of Schistosomiasis
R. S. Díaz-Rivera, M.D.; F. Ramos-Morales, M.D.; Z. R. Sotomayor, M.D., and Sylvia Santiago, M.D., San Juan, P. R. 1151

EVOLUTION OF MODERN MEDICINE

A Bibliography of Internal Medicine
Arthur L. Bloomfield, M.D., San Francisco 1159

BOOKS

Reviews by Dr. William B. Bean and Others 1172

REGULAR DEPARTMENTS

News and Comment 1181

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 101 JUNE 1958 NUMBER 6

COPYRIGHT, 1958, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

PAUL S. RHOADS, Chief Editor, Chicago

WILLIAM B. BEAN, Iowa City
ARTHUR BLOOMFIELD, San Francisco
GEORGE E. BURCH, New Orleans
HUGH R. BUTT, Rochester, Minn.
CHARLES S. DAVIDSON, Boston
LOUIS LEITER, New York
BRUCE K. WISEMAN, Columbus, Ohio

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $10.00. Canadian, $10.50. Foreign, $11.50. Price to students, interns, and residents, $6.00 in U. S. & possessions.

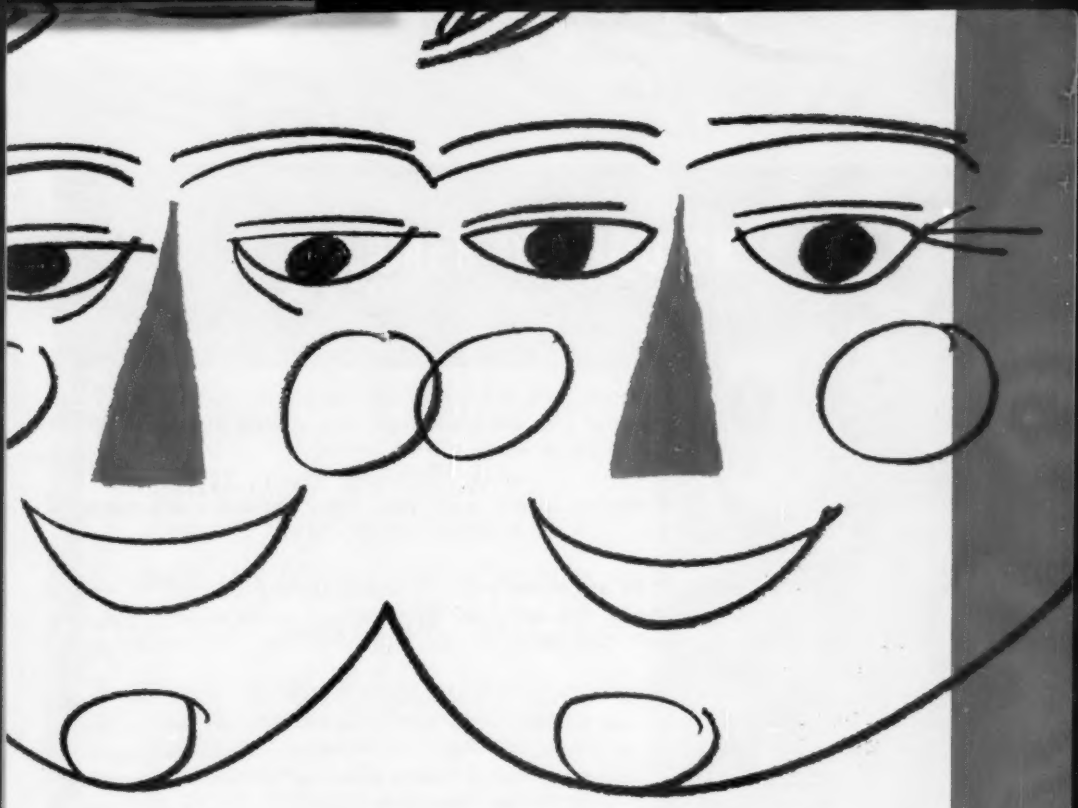
Single copies of this and previous calendar year, $1.00.

Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.



doubles decongestion benefits...

in colds, sinusitis, allergic or vasomotor rhinitis as well as in allergic congestion of the lower respiratory tract

new formula
CHLOR-TRIMETON Compound

orally effective decongestant **R E P E T A B S**

interlocking action for more rapid and pronounced relief

- Combines the benefits of CHLOR-TRIMETON with phenylephrine, decongestant with negligible side effects.
- Additive effect of combined components provides more pronounced and longer-lasting relief from nasal and bronchial congestion.
- Unique REPETAB prolongs relief and maintains it at a sustained, uninterrupted therapeutic level.

Formula—Each CHLOR-TRIMETON Compound REPETAB contains 4 mg. chlorprophenpyridamine maleate and 20 mg. phenylephrine equally divided between outer layer and inner core separated by a timed disintegration barrier.

Dosage—One REPETAB two or three times daily as required. *Supplied*—Bottle of 100.

CHLOR-TRIMETON® Maleate, brand of Chlorprophenpyridamine Maleate U.S.P.
REPETABS,® Repeat Action Tablets.

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

CTM-J-210

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

AN AMES CLINIQUICK

CLINICAL BRIEFS FOR MODERN PRACTICE

what liver metabolites, commonly considered always toxic, are actually a vital source of energy?

"Ketone" bodies—*acetoacetic acid, acetone* and *β-hydroxybutyric acid.* Despite their potential for harm, they are normal intermediate products in the catabolism of fatty acids and represent a "quick fuel" to the cells in the same manner as glucose. They are toxic when produced faster than utilized, appearing in the urine as an abnormal finding—ketonuria.

Source—Hoffman, W. S.: The Biochemistry of Clinical Medicine, Chicago, The Year Book Publishers, Inc., 1954, p. 95.

KETOSTIX TRADEMARK *Reagent Strips*

dip-and-read test for ketonuria

specific • standardized • sensitive

greater relative sensitivity to acetoacetic acid—the more reactive ketone

Supplied: bottles of 90 KETOSTIX Reagent Strips—No. 2391

for tablet testing—ACETEST® Reagent Tablets detect ketone bodies with one drop of urine

AMES COMPANY, INC • ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto 49380

Just Published:

Volume 9 of the ANNUAL REVIEW OF

MEDICINE

"The usual high standard of former issues for reporting medical developments has been maintained. . . . Contributors are dependably expert, as always." *JNL. of Medical Education, Sept. 1957*

". . . continues in the best traditions of this distinguished series." *The Am. Jnl. of Clinical Nutrition, Vol. 5, No. 5, 1957.*

CONTENTS: **530 pages**

EDITOR:
D. A. Rytand

ASSOCIATE EDITOR:
W. P. Creger

EDITORIAL COMMITTEE:
R. E. Cooke
W. C. Cutting
G. J. Dammin
M. A. Hayes
C. G. Loosli
D. A. Rytand

ALSO AVAILABLE:
Volumes 1 to 8

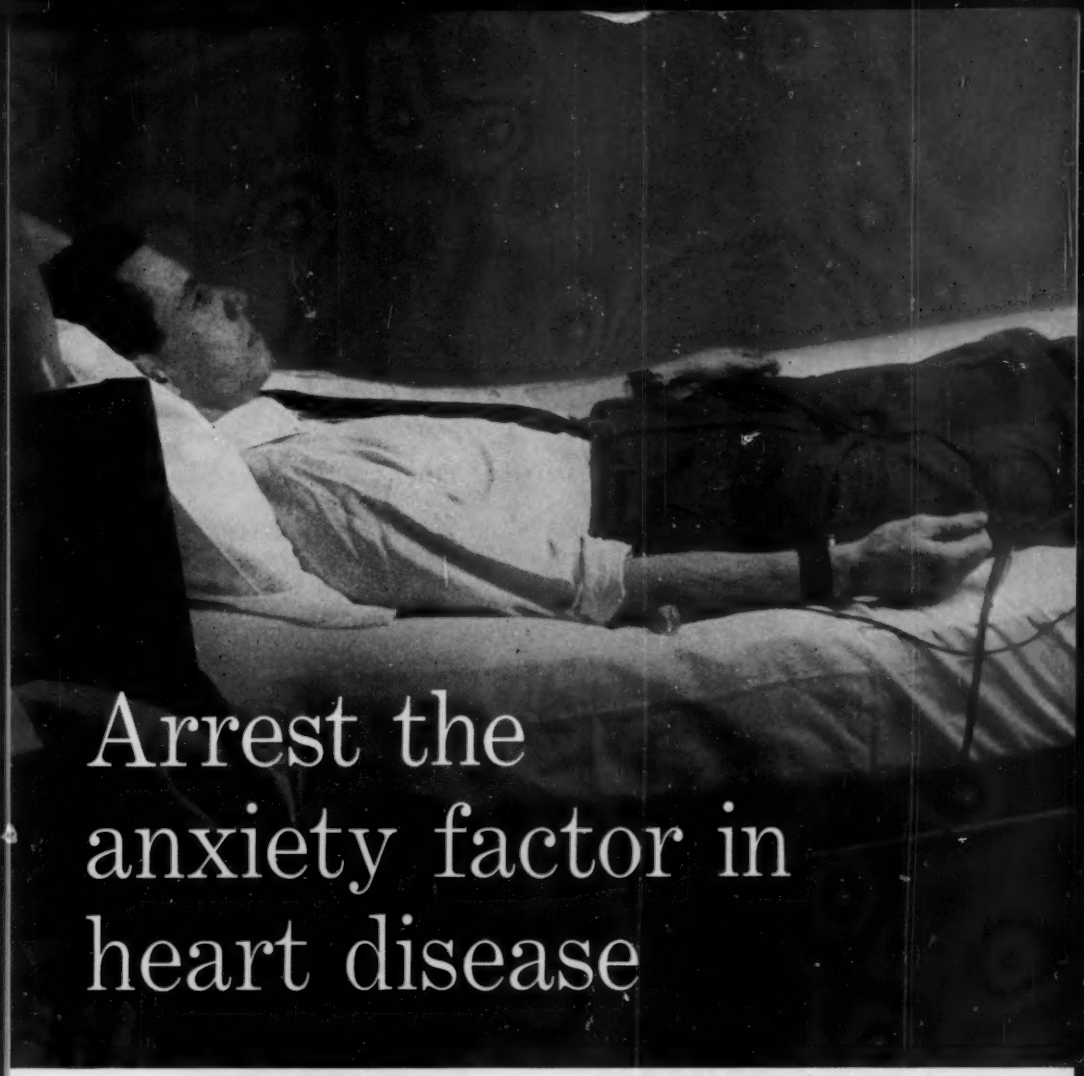
PRICE:
$7.00 postpaid (USA)
$7.50 postpaid (elsewhere)

Infectious Diseases (Bacterial), *E. M. Yow and R. D. Leachman*
Fungal Infections and Chemotherapy, *W. D. Sutliff*
Infectious Disease (Viruses), *F. M. Burnet and E. L. French*
Diseases of the Gastrointestinal Tract, *H. M. Pollard, R. J. Bolt, A. B. French, L. O. Standaert, and R. C. King*
Cardiovascular Diseases (Medical), *R. P. Grant and S. M. Fox, 3rd*
Diseases of the Aorta, *S. H. Boyer, IV and V. A. McKusick*
Cardiovascular Diseases (Surgical), *O. C. Julian, W. S. Dye, and H. Javid*
Diseases of the Kidney (Medical), *H. D. Lauson*
Diseases of the Kidney (Surgical), *W. F. Leadbetter*
Hemostatic Disorders: Hemophilia and the Hemophilioid Diseases, *K. M. Brinkhous, R. D. Langdell and R. H. Wagner*
Nutrition and Nutritional Deficiency Diseases, *R. W. Vilter and J. J. Will*
Endocrinology, *S. P. Asper, Jr. and E. H. Wilson, Jr.*
Allergy and Immunology: Autoimmunity in Disease, *F. J. Dixon*
Neoplastic Diseases (Cancer), *C. G. Zubrod*
Diseases of the Nervous System, *W. O. Klingman*
Psychiatry, *R. A. Cleghorn*
Drug Actions Upon the Brain "Psychopharmacology," *J. D. French*
Clinical Evaluation of Drugs, *L. Lasagna and P. Meier*
Diagnostic Radiology, *F. J. Hodges*
Toxicology of Radioactive Materials, *H. Foreman*
Diseases of the Skin, *A. L. Lorincz and S. Rothman*
Pediatrics, *H. K. Faber, R. H. Alway, R. T. Gross, L. Luzzatti, J. J. Osborn, C. F. Piel and E. H. Senz*
Diseases of the Bones and Joints, *W. Graham and R. Moore*
Plastic Surgery: Homotransplantation, Congenital Anomalies, Wound Healing, and Skin Storage, *B. Cannon*
Dentistry, *B. E. Gustafsson*
Laboratory Aids to Diagnosis and Therapy (Paper Chromatography and Electrophoresis), *E. L. Durrum*
Laboratory Aids to Diagnosis and Therapy (Enzymes), *H. A. Harper*
Soviet Medical Research: Some Recent Advances and Future Plans, *A. Shelokov*

Published March, 1958: ANNUAL REVIEW OF PHYSIOLOGY Vol. 20

V. E. Hall, F. A. Fuhrman, A. C. Giese, Editors; 633 pages

ANNUAL REVIEWS, INC.,
231 Grant Avenue, Palo Alto, California, U.S.A.



Arrest the anxiety factor in heart disease

without affecting autonomic function

"A cardiac breakdown might be forestalled or arrested" by effective treatment of nervous tension and anxiety.* Adjunctive therapy with meprobamate "definitely reduced nervous tension and anxiety" in all heart patients (80 cases), and enhanced recovery from acute cardiac episodes in many cases.*

**Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.*

Because of its unexcelled safety, *Miltown is well suited for tranquilization of chronic heart patients. It is well tolerated, relatively nontoxic, and produces no blood dyscrasias, liver impairment, parkinsonism, or nasal stuffiness. It does not mask toxicity of other drugs.*

Miltown®

Miltown is the original *meprobamate, discovered and introduced by* ® WALLACE LABORATORIES *New Brunswick, N. J.*

CM-6079

It Fits...

Regardless of the diet

your patient requires...

low fat...low calorie...

restricted fiber...high

protein...bland...

or low purine...

Enriched Bread

is basic, integral, compatible, easily digested, low in fat, virtually free from fiber... an excellent vehicle for other foods.

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive Chicago 6, Illinois

in the peptic-ulcer regimen

ACID NEUTRALIZATION
is fundamental

"In all essential respects subsequent investigations have corroborated the original concept of Sippy [acid neutralization]."[1]

1. Cecil, R.L., and Loeb, R.F.: A Textbook of Medicine. W.B. Saunders Co., Philadelphia, 1955, 9th ed., p. 870.

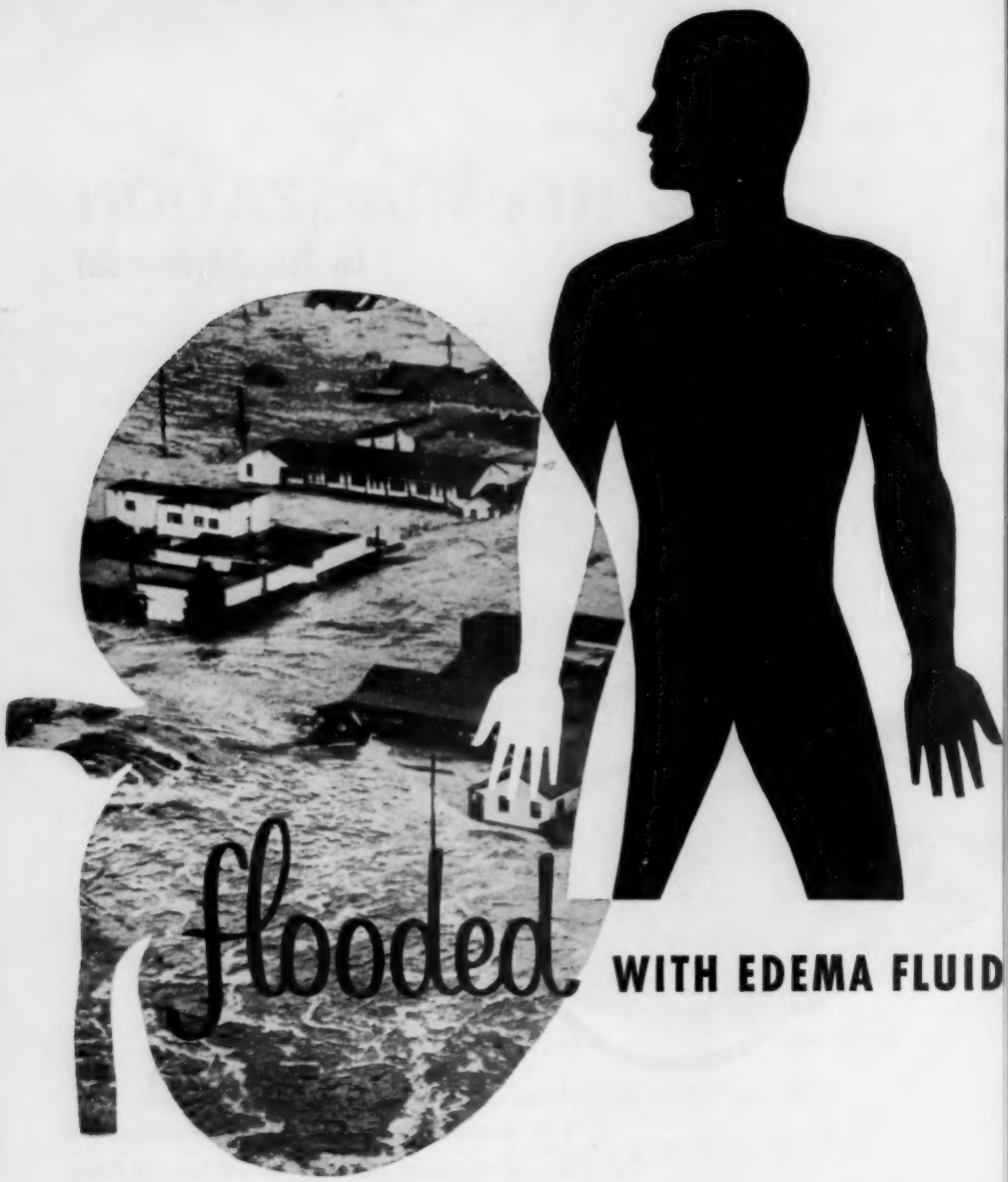
FUNDAMENTAL THERAPY IN PEPTIC ULCER

Wyeth®
Philadelphia 1, Pa.

AMPHOJEL®

double gel
for diphasic action

Aluminum Hydroxide Gel, Wyeth



WITH EDEMA FLUID

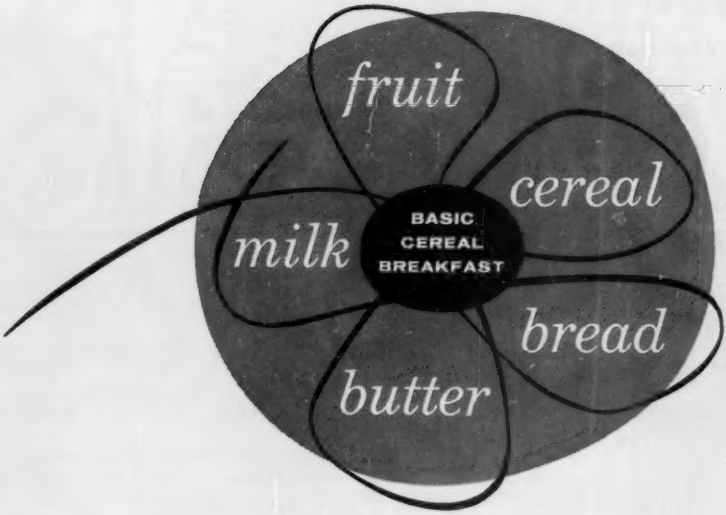
SALYRGAN®-THEOPHYLLINE

drains off edema fluid in nephrosis, hepatic cirrhosis and congestive failure. By eliminating massive amounts of fluid, Salyrgan-Theophylline reduces the load placed upon the heart and increases cardiac efficiency.

Winthrop LABORATORIES
NEW YORK 18, N. Y.

Ampuls of 1 cc. and 2 cc. Enteric coated tablets.

Salyrgan (brand of mersalyl), trademark reg. U.S. Pat. Off.



what is a well-balanced *low-fat* quick and lasting energy breakfast?

What is meant by "Quick and Lasting Energy"? It is a prompt "lift" due to a quick rise in blood sugar—a lasting "lift" due to the fact that the blood sugar remains up and falls only gradually during the late morning hours.

The Iowa Breakfast Studies demonstrated that a basic cereal and milk breakfast as shown below provided quick and lasting energy. This basic breakfast is *low in fat* and makes a well-balanced contribution of the essential nutrients.

basic cereal low-fat breakfast pattern

Orange juice, fresh, ½ cup,
Cereal, dry weight, 1 oz.,
with whole milk, ½ cup, and sugar, 1 tsp.,
Bread, white, 2 slices, with butter, 1 tsp.,
Milk, nonfat (skim), 1 cup,
black coffee

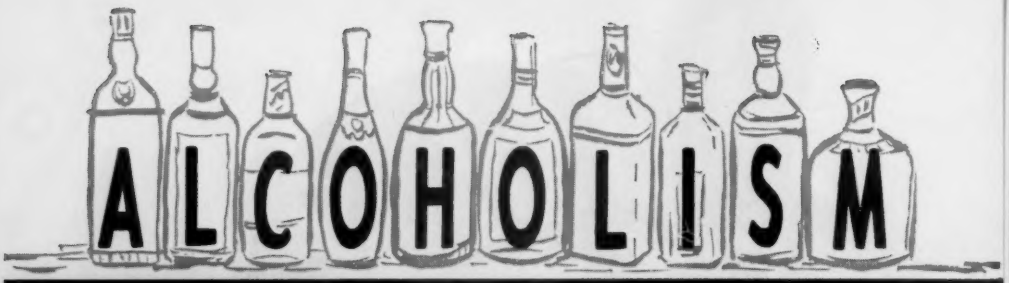
Nutritive value of basic cereal breakfast pattern

CALORIES	502	VITAMIN A	600 I.U.
PROTEIN	20.5 gm.	THIAMINE	0.46 mg.
FAT	11.6 gm.	RIBOFLAVIN	0.80 mg.
CARBOHYDRATE	80.7 gm.	NIACIN	3.0 mg.
CALCIUM	0.532 gm.	ASCORBIC ACID	65.5 mg.
IRON	2.7 mg.	CHOLESTEROL	32.9 mg.

Note: To further reduce fat and cholesterol use skim milk on cereal which reduces Fat Total to 7.0 gm. and Cholesterol Total to 16.8 mg. Preserves or honey as spread further reduces Fat and Cholesterol.

Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.
Cereal Institute, Inc.: A Summary of the Iowa Breakfast Studies. Chicago: Cereal Institute, Inc., 1957.

CEREAL INSTITUTE, INC. 135 South LaSalle Street, Chicago 3
A research and educational endeavor devoted to the betterment of national nutrition



an important problem in today's living...

The following articles from TODAY'S HEALTH are now available in pamphlet form.

ALCOHOLISM IS A DISEASE. A discussion by the Chairman of the A.M.A. Committee on Alcoholism. by Marvin A. Block, M.D., 8 pages, 15 cents.

I AM THE WIDOW OF AN ALCOHOLIC. Three articles combined. by Virginia Conroy, 16 pages, 20 cents.

HOW EXPERTS MEASURE DRUNKENNESS. A partial transcript of an actual courtroom case. by H. A. Heise, 8 pages, 15 cents.

BARBITURATES, BOOZE AND OBITUARIES. A discussion of the dangers of mixing alcohol and barbiturates. by Donald A. Dukelow, 4 pages, 10 cents.

TWELVE STEPS FOR ALCOHOLICS. A frank discussion of the meaning of an alcoholic behavior. by Richard Lake, 6 pages, 10 cents.

These articles are available in one pamphlet for 50c

ALCOHOLICS ANONYMOUS. Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.

ALCOHOL AND CIRRHOSIS OF THE LIVER. Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences. by Russell S. Boles.

HOW TO HELP A PROBLEM DRINKER. Understanding the alcoholic's capabilities, the necessity of help, causes of his condition. by Edward A. Strecker and Francis T. Chambers, Jr.

THE TREATMENT OF ALCOHOLISM. Tracing the steps from convincing the alcoholic that he is sick through treatment and cure. by Lewis Inman Sharp.

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM. Its place among methods of treatment today, its development and correlation with personality factors. by Walter L. Voegtlin.

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM. Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel. by E. H. L. Corwin.

ADDRESS REQUESTS TO

ORDER DEPARTMENT
AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST., CHICAGO 10, ILLINOIS

RETURN PATIENTS TO CONSCIOUSNESS FROM...

hepatic coma

associated with high blood ammonia levels

GLUTAVENE®

&

GLUTAVENE-K®

For the treatment of coma and other encephalopathies in certain liver diseases associated with high blood ammonia levels, Glutavene supplies monosodium l-glutamate and Glutavene-K supplies monosodium and monopotassium l-glutamate. These agents reduce ammonia blood levels through amidation, a reaction between glutamate and ammonia to form glutamine, a nontoxic substance.[1,2]

administration: For the average adult, 100 pounds or over, the contents of a 100 cc. (25 gram) vial are mixed with 1000 cc. of 5 or 10% glucose in water. This amount is given intravenously during a 4-hour period.

References: 1. McDermott, W. V., Jr.; Waravdekar, V., and Riddell, A. G.: New England J. Med. 253:1093 (Dec. 22) 1955. 2. Watson, C.: J.A.M.A. 166:764 (Feb. 15) 1958.

CROOKES-BARNES LABORATORIES, INC.
Wayne, New Jersey

Of interest to you and your patients

THE MENACE OF ALLERGIES

WHAT WE KNOW ABOUT ALLERGY
by Louis Tuft, 12 pages, 15 cents

HOUSE DUST ALLERGY
by Karl D. Figley, 8 pages, 15 cents

FOOD ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

SKIN ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

ASTHMA AND HAY FEVER
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

RAGWEED AND HAY FEVER
by Oren C. Durham, 2 pages, 5 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10 • ILLINOIS

when your depressed patient is also tense and anxious

Dexamyl* Tablets
'Dexedrine' (5 mg.) plus amobarbital (½ gr.)

relieve depression, and replace tension and anxiety with a feeling of confidence and well-being

Also available: Elixir and Spansule* sustained release capsules.

*T.M. Reg. U.S. Pat. Off.

when your depressed patient is also listless and lethargic

Dexedrine* Tablets, 5 mg. Smith Kline & French Laboratories, Philadelphia
dextro-amphetamine sulfate, S.K.F.

relieve depression, and replace listlessness and lethargy with a feeling of energy and optimism

Also available: Elixir and Spansule* sustained release capsules.

Intravenous Cholangiography: a need fulfilled

"...the need for a contrast medium that would be of uniform and reliable visualization for all the ducts, especially in the patients having had cholecystectomy, was not met until the introduction of Cholografin."[1]

"...a reliable method for rapid visualization of the biliary tract irrespective of whether or not the gallbladder is present and independent of its ability to concentrate its contents."[2]

CHOLOGRAFIN

SQUIBB IODIPAMIDE

for reliable, rapid intravenous cholangiography and cholecystography

- the entire extrahepatic biliary system is visualized even in many postcholecystectomy patients and in the presence of a nonfunctioning gallbladder
- the gallbladder is visualized, even if diseased, unless there is obstruction of the cystic duct
- makes possible rapid diagnosis
- well tolerated

SUPPLY:

Cholografin Sodium: 2 x 20 cc. ampuls, each with 1 cc. ampul for sensitivity testing.

Cholografin Methylglucamine: 20 cc. ampuls with 1 cc. ampul for sensitivity testing.

1. Reeves, R. J.: Southern M. J. 50:1377 (Nov.) 1957.
2. Shehadi, W. H.: Am. J. Gastroenterol. 28:236 (Sept.) 1957.

"CHOLOGRAFIN"® IS A SQUIBB TRADEMARK

SQUIBB
New York 22, N. Y.

Squibb Quality—
the Priceless Ingredient

Surgical Results in Coarctation of the Aorta, Aortic Stenosis, and Pulmonary Stenosis

The surgical relief of obstruction at the valves of the heart and in the great vessels has been widely practiced for the last 10 years and has proved most successful. I am discussing the present position for patients with pulmonary stenosis, aortic stenosis, or coarctation of the aorta. The question is approaching a definitive answer for pulmonary stenosis and coarctation but not for aortic stenosis. I am reviewing our own experience at Guy's Hospital, London, rather than experience at other centers, but think they are in general agreement; this has the advantage that all the patients in the series referred to have been studied by me.

Coarctation of the Aorta

Most patients with coarctation feel well and can lead a normal life, but its presence carries serious hazards, especially in the third decade—hazards of aortic rupture, of intracranial hemorrhage from a berry aneurysm, and of subacute bacterial endocarditis. The blood pressure generally rises in the first two decades, from an average of 145/90 at 5 years to 190/105 at 17 years, and then remains relatively stable. About 1 patient in 4 has aortic regurgitation, generally from bicuspid aortic valves, and about 1 in 20 has aortic stenosis that is probably congenital; these add to the risk of congestive heart failure which is an increasing hazard from the third decade onward.

All patients should, therefore, have surgical treatment in childhood unless the rise of blood pressure is trivial. A few infants with coarctation develop congestive heart failure in the first year of life, and here operation should be done at once. I have little personal experience of this type, and it is uncertain how far the aorta will remain unobstructed after operation at such an early age. The great majority of infants and children do well, and it is generally best to defer operation till the age of 7 years. In older patients, between 20 and 30, the increased risk of operation is not as great as was thought, but in patients over 30 a more conservative attitude should be taken, for the third decade seems to be the period of greatest danger. The operation has now become reasonably safe, with a mortality approaching 5%.

The results are good in the hands of a skilled surgeon, and the pressure falls, sometimes to normal but more often to a little above this. This settles a long discussion about the cause of the raised pressure. Most of the rise proximal to

Submitted for publication Jan. 31, 1958.

the obstruction must be a simple mechanical effect, but it is still uncertain whether the slighter rise that often remains is because secondary irreversible changes had developed or because the resection and anastomosis has not produced a lumen of adequate size.

Forty consecutive patients in whom an anastomosis was completed, more than half between 10 and 24 years and a quarter over this age, have now been followed for from 2 to 10 years. They include those discussed in more detail by Campbell and Baylis (1956) and have now been followed for longer. Those who had symptoms have been relieved, but often the symptoms were so slight that a fall of the high blood pressure is the only useful measure of improvement. This has, with two exceptions, become much lower; the average fall was from 180/105 to 140/85 mm., and this has been maintained. Only one has a diastolic pressure above 95 mm. but over a quarter have one of about 90 mm. Signs of left ventricular strain in the electrocardiogram generally diminish. Though as a rule, the left ventricle is enlarged, the heart generally is not, so that any diminution in size is difficult to measure.

Slight aortic regurgitation is an extra reason for surgical treatment, since it is likely to be progressive without operation, but gross regurgitation is a contra-indication. With intermediate degrees the relief of one load on the left ventricle may help for a time, but the operation has been left too late to obtain a good result. Thus, in one girl a diastolic murmur that was generally heard before operation has not been heard since, and one man with moderate regurgitation that remains unchanged is much better and able to do more. On the other hand, a young man with gross regurgitation was not helped, for though the blood pressure was lower, he died with left ventricular failure a year later.

The reduction of blood pressure must diminish the risk of cerebral hemorrhage, of aortic rupture, and of developing aortic regurgitation and probably the risk of bacterial endocarditis. Only the passage of time, however, can tell how effectively it will remove these risks, though so far the reported results are encouraging. It is, therefore, important that all these patients should be kept under observations for the next 20 years.

Aortic Stenosis

The problem with aortic stenosis is more difficult than with stenosis of the other valves. The valve is, as a rule, greatly deformed and calcified, and so it may be impossible for the surgeon to enlarge the opening without producing regurgitation. Often there is already significant regurgitation, and then it is unlikely that the patient's life can be lengthened by making the opening larger, even though he may feel better and may be able to do more for a time. Aortic regurgitation is more serious than pulmonary regurgitation because with the higher pressure any failure of the valve to close may lead to free regurgitation.

In the rheumatic cases of aortic stenosis (generally associated with mitral stenosis) these points are less serious, for the valve is less often calcified and less grossly deformed. Generally the mitral obstruction is more important, but when there is a gradient of 60 mm. or more across the aortic valve, aortic valvotomy is indicated and is often successful.

In the congenital cases in children and in the calcified cases that often have developed on a slight congenital stenosis, mostly in men over 40, the problem is more difficult and the results are less good. Even in children, where calcification is unlikely, the valve is generally irregular and deformed, though sometimes it is dome-shaped and smoother, like the valve of pulmonary stenosis.

The outlook for these congenital cases without operation is, however, worse and more uncertain than we thought at one time; sudden death, sometimes with no obvious warning or sometimes after attacks of syncope or angina is not rare (Campbell and Kauntze, to be published, and Braverman and Gibson, 1957). Operation must, therefore, be considered carefully. Even when a patient says he is well and has few symptoms, he should be asked if vigorous exercise can produce any sternal tightness or faintness, for these are dangerous signs. For example, one girl said that she led a normal life and could run upstairs at school as well as others but admitted that after energetic dancing she had characteristic midsternal pain; this, with slight cardiographic deterioration, was regarded as an indication for operation.

Left ventricular puncture to measure the gradient across the aortic valve is of great help and appears to be reasonably safe. It also helps to assess the relative importance of aortic regurgitation in a doubtful case (Fleming and Gibson, 1957).

In our experience the results are not good enough to advise operation unless there is some danger signal, either in congenital or in calcific aortic stenosis, though patients with the latter have less chance of a long life without operation. Baker and Campbell (1956), reporting a short series of cases, found that in one-third good results were obtained, one-third were improved, but one-third died; even so, not all the good results have been maintained. Brock (1957) has recently reported on his results more optimistically, but although more of our patients operated on since 1956 have been younger, the results have not improved enough to make us modify our views substantially.

Simple Pulmonary Stenosis

Pulmonary valvular stenosis with a closed ventricular septum can be greatly relieved by surgery, whether there is a right-to-left shunt through an unsealed foramen ovale or not. This is also true of the rarer infundibular stenosis. My experience with 70 patients is very good, and the results reported by Campbell and Brock (1955) have been extended and maintained.

Usually after operation, a severe stenosis is changed to a slight or moderate one that is not of great importance. The pressure in the right ventricle is reduced to one-third or one-half of its previous level. If there is a reversed shunt, this is generally cured and the patient loses his cyanosis. If the heart was enlarged, it becomes smaller, on an average by 10% in diameter, and the signs of right ventricular strain diminish or even disappear. Pulmonary regurgitation is not often produced by operation and, when it is, does not as a rule prevent improvement, but it must be a disadvantage in the long view. Sometimes the reduction in the gradient as measured at operation may seem disappointing because of functional infundibular stenosis from the great hypertrophy of the muscle. But a year or so later catheterization generally shows that this improves and sometimes

disappears completely when there has been a successful valvotomy. The follow-up of these patients, some for nine years, does not reveal any tendency for the stenosis to recur.

My experience is mostly with closed operations, and the earlier open operations had the drawback that they were often followed by pulmonary regurgitation. This, however, has been overcome, and recent cases of Sir Russell Brock and the latest report of Blount et al. (1957) show that on the whole even more relief can be obtained in this way, most patients being cured or almost cured of their pulmonary stenosis.

Pulmonary Stenosis with Ventricular Septal Defect—Fallot's Tetralogy

Fallot's tetralogy can be treated by subclavian-pulmonary anastomosis or by Brock's direct operation of valvotomy and infundibular resection. Both these are less curative than valvotomy for simply pulmonary stenosis, for the ventricular septal defect and the right ventricular hypertrophy remain. Nevertheless, the improvement in capacity and in the cyanosis is enormous, and many of 300 patients seen are able to earn a living and lead a quiet normal life.

Anastomotic Operations for Fallot's Tetralogy.—In the earlier report that included the results for up to four years after operation, nearly all the patients who achieved good results had maintained them (Campbell and Deuchar, 1953). During the subsequent four years I became less optimistic, for several returned to hospital having relapsed. A further follow-up has, however, brought me back nearer my original view, for I had seen nearly all the patients who were doing badly but few of those who were doing well, as they were carrying on happily and feeling no need to attend the hospital.

Good results were obtained in 130 of the first 165 patients, and 121 of the 130 have been traced; 99 (82%) are still as good or nearly as good as they were, but 18% have lost much or all of their improvement after an average period of 7 years (range, 5 to 10 years), about 3% per annum. A few are included as good results, because the improvement from their previous state is so great, although they cannot lead a normal life or have some residual disability, e. g., from a cerebral thrombosis. A few find it difficult to work because they are not intelligent enough to overcome their past lack of schooling. A few have had a second operation, not because they had lost their improvement but because their disability had been so severe that they were still very handicapped. Five of these patients had bacterial endocarditis during the seven years, but all made a good recovery. Good follow-up results have been reported by White et al. (1956) also.

The patients who obtained good results but have since lost ground are important. Seven have died. One girl, aged 7, died unexpectedly of pulmonary edema, and a woman, aged 20, died suddenly in the street, 37 and 18 months, respectively, after operation. One died with nephritis in the sixth year. Three boys died of cerebral abscesses, one in the 3d and two in the 10th years after operation. My oldest patient died when he was 43 with carcinoma of the bronchus in the eighth year. Nearly all these patients remained in good health till their terminal illness.

In addition to those who died, 11 patients have lost all their improvement and 4 have lost a good deal of it. This was caused by the closing of the anastomosis

in the eight, for the continuous murmur could no longer be heard; presumably they reverted to just the same condition as before operation. In two others the anastomosis was probably carrying less blood, as the murmur was more difficult to hear. There were, however, five who lost ground, although the continuous murmur could be heard as well as before; I think they were showing the natural tendency of patients with Fallot's tetralogy to become worse, either from increasingly severe stenosis, which is most likely at these ages, or sometimes from increasing right ventricular strain. Some of these patients have since had direct operations, but I find that second operations have a higher mortality and are less successful as regards the degree of improvement.

Direct Operations.—The immediate mortality of direct operations is higher, 17% for all our patients but under 10% if we exclude operations before 1952 and second operations. The proportion who obtained only a little improvement is about the same (12%), and this has become less since the fuller realization of the frequency and importance of the infundibular stenosis often associated with valvular stenosis. The good results (71%) (Campbell et al., 1954) are at least as good as those obtained by anastomotic operations, and more patients are completely relieved from their cyanosis, often at the expense of a left-to-right shunt through the ventricular septal defect, with possible disadvantages for the future. I have, however, seen only two patients, and one of these was after an anastomotic operation, where the left-to-right shunt has been large enough to lead finally to heart failure.

The good results have been well maintained in my recent follow-up by 90% of the patients; few have relapsed, and very few have died. They seem to have no greater tendency to get worse—perhaps less—than patients who have had no operation. There are few with any evidence that the stenosis has got worse again, whether the operation was infundibular resection or valvotomy.

This more lasting improvement balances the higher operative mortality, and as this is reduced, direct operations seem likely to produce a lasting good effect in a larger number of patients than anastomotic operations. The only qualification of this is that a longer follow-up is needed, for most of the patients who had an anastomotic operation were excellent after four or five years, and it was mainly in the 6th to 10th years that the anastomosis closed in a significant number.

Those who have had direct operations have been followed for an average of 4.7 years only, but none of the 20 who have been followed for more than 7 years seems to be losing ground. The present position is that 65% of all the patients who had anastomotic operations and 63% of those who had direct operations are still maintaining good results after 7 and 4.7 years, respectively. It remains to be seen whether curative operations with closure of the ventricular septal defect can equal or improve on these results. There seems little doubt that this will happen if the operative mortality can be greatly reduced.

MAURICE CAMPBELL, O.B.E., D.M., F.R.C.P.
47 Arkwright Rd.
Hampstead
London N. W. 3

BIBLIOGRAPHY

Baker, C. G., and Campbell, M.: The Results of Valvotomy for Aortic Stenosis, Lancet 1:171, 1956.

Blount, S. G., Jr.; Van Elk, J.; Balchum, O. J., and Swan, H.: Valvular Pulmonary Stenosis with Intact Ventricular Septum, Circulation 15:814, 1957.

Braverman, I. B., and Gibson, S.: The Outlook for Children with Congenital Aortic Stenosis, Am. Heart J. 53:487, 1957.

Brock, R.: Surgical Treatment of Aortic Stenosis, Brit. M. J. 1:1019, 1957.

Campbell, M., and Baylis, J. H.: The Course and Prognosis of Coarctation of the Aorta, Brit. Heart J. 18:475, 1956.

——— and Brock, R.: The Results of Valvotomy for Simple Pulmonary Stenosis, Brit. Heart J. 17:229, 1955.

——— and Deuchar, D.: Results of the Blalock-Taussig Operation in 200 Cases of Morbus Caeruleus, Brit. M. J. 1:349, 1953.

——— Deuchar, D., and Brock, R.: Results of Pulmonary Valvotomy and Infundibular Resection in 100 Cases of Fallot's Tetralogy, Brit. M. J. 11:111, 1954.

Fleming, P., and Gibson, R.: Percutaneous Left Ventricular Puncture in the Assessment of Aortic Stenosis, Thorax 12:37, 1957.

White, D. B.; McNamara, D. G.; Bauersfeld, S. R., and Taussig, H. B.: Five-Year Post-Operative Results of First 500 Patients with Blalock-Taussig Anastomosis for Pulmonary Stenosis or Atresia, Circulation 14:512, 1956.

A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Functional Isosthenuria

An Isolated Reversible Renal Tubular Defect

CHARLES R. KLEEMAN, M.D.; MORTON H. MAXWELL, M.D., and STEVEN WITLIN, M.D., Los Angeles

True polyuria and polydipsia are symptoms frequently encountered in clinical medicine. Generally they indicate a serious organic disorder which must be systematically investigated for prompt and adequate diagnosis. Table 1 represents a schematic presentation of the major polyuric syndromes. In all instances the symptom arises whenever there is a *decrease* in the per cent of the water normally reabsorbed from the glomerular filtrate. As can be seen, this results from (1) a decrease in the reabsorption of water per se, (2) a decrease in the reabsorption of solutes, with, therefore, an obligatory excretion of water (absolute or relative osmotic diuresis *), or (3) a combination of one and two.

Submitted for publication Oct. 31, 1957.

From the Department of Medicine, University of California Medical Center and Veterans' Administration Center. Chief, Metabolic Service, Veterans' Administration Hospital, and Associate Clinical Professor of Medicine, University of California Medical Center (Dr. Kleeman); Associate Clinical Professor of Medicine, University of California Medical Center (Dr. Maxwell); Intern, Medical Service, Veterans' Administration Hospital (Dr. Witlin).

* The term "relative osmotic diuresis" is used here to refer to the polyuria secondary to a reduction in functioning renal mass. In this state, the normal daily excretion of solutes must be accomplished with a reduced number of nephrons. Therefore each nephron carries a relatively large osmotic load, and this results in a relative osmotic diuresis.

TABLE 1.—*The Major Polyuric Syndromes*

Water	Excessive H_2O ingestion	Psychogenic polydipsia Postencephelitic polydipsia (rare)
	Inability to reabsorb adequate amounts of filtered H_2O	Absent vasopressin = diabetes insipidus Renal tubular failure to respond to vasopressin 1. Nephrogenic diabetes insipidus (congenital and familial) 2. Nephrogenic diabetes insipidus (acquired) (*a*) Usual chronic renal diseases (*b*) Obstructive uropathy (*c*) Multiple myeloma (*d*) Potassium deficiency (*e*) Hyperaldosteronism (*f*) Nephrocalcinosis or renal damage secondary to hypercalciuria (*g*) Unilateral renal artery occlusion
Solutes; inability to reabsorb adequate quantities of filtered solutes (osmotic-type diuresis)	Glucose—diabetes mellitus	
	Salts—primarily sodium chloride	(*a*) Various types of chronic renal disease, particularly chronic pyelonephritis (*b*) After various diuretics, particularly mercurials

Recently a case was observed which, while classifiable, presented features which to our knowledge had not been previously described. This patient, an example of long-standing psychogenic polydipsia, was initially unable to concentrate his urine above the osmolality of his extracellular fluid, in spite of the absence of any other evidence of renal impairment. It has been generally held that psychogenic polydipsia can be differentiated from the other polyuric syndromes listed (Table 1) by the ability to form a concentrated urine when rigorous restriction of water is imposed (response to endogenous antidiuretic hormone [ADH]) and/or following the exogenous administration of antidiuretic hormone (vasopressin [Pitressin]).

Recent experiments by Epstein, Kleeman, and Hendrikx [1] have demonstrated that normal subjects are unable to concentrate their urine maximally in response to a standardized infusion of vasopressin after they have been maintained for a three-day period with water loads of 5 to 7 liters per day. The "defect" in concentration clears quickly after return to a normal ad libitum volume of water ingestion. The present case would appear to represent a more marked clinical example of this functional defect.

Report of a Case

The patient, a 48-year-old white man was admitted in July, 1956, with a history of intermittent polyuria and polydipsia since the age of 13 or 14 that began after a febrile illness with delirium which lasted for approximately one week. These symptoms persisted with varying intensity until 1942, at which time they subsided spontaneously for a brief period after his induction into the army. Polyuria and polydipsia gradually recurred, however, and he was discharged in 1945, with a possible diagnosis of diabetes insipidus. For a period of five to seven years he took posterior pituitary extract by nasal inhalation with little, if any, benefit. During the three-year period prior to admission, he received no specific therapy other than one two-week course of vasopressin tannate in oil, which he felt had considerably reduced his urine volumes approximated 8 to 9 liters, and intake and output of water were approximately 7 to 10 qt. daily.

His past history was noncontributory. He had no other symptoms referable to his urinary tract His family history was negative with regard to any similar polyuric or polydipsic syndromes.

Physical examination was entirely normal, with the exception that the patient was continuously licking his lips and opening his mouth at intervals, as though about to sneeze.

Routine Laboratory Data.—Repeated routine urinalyses were entirely normal, and numerous midstream urine cultures revealed no bacteriuria. Blood cell counts and spinal fluid examination were within normal limits. Serologic tests for syphilis were negative. X-rays of his skull and chest were normal, and a K. U. B. examination did not disclose any abnormal configuration of the renal shadows or intrarenal calcification. An intravenous pyelogram showed good concentration of the dye in the renal pelves, with normal pelvic and calyceal systems. Retrograde pyelograms were also considered negative.

Hospital Course and Further Laboratory Investigations.—For the first week of hospitalization, the patient ate and drank *ad libitum*. His daily urinary volume. He estimated that his average random specific gravity determinations never exceeded 1.005. He rarely got up during the night to void.

On three occasions during the second week of hospitalization, the patient was subjected to a standard 16-hour period of complete fluid restriction. Following one of these periods, he also received an infusion of vasopressin (200 milliunits per hour) for an additional four-hour period. Although urine volume consistently decreased to 1.5 to 2.5 cc. per minute during these tests, the maximum specific gravity did not exceed 1.009, and urinary osmolality, measured by freezing-point depression with a Fiske Osmometer, did not exceed 300 mOsm. per liter. The osmolality of his serum ranged from 287 to 311 mOsm. per liter.

It was readily apparent from the above concentration tests that the patient's ad libitum ingestion of water was greatly in excess of that required for the obligatory excretion of his daily urinary solutes. This strongly suggested a psychogenic polydipsia, but it was essential to rule out other renal tubular lesions (Table 1) which could produce a similar concentrating defect. In Table 2 are listed chemical determinations of his blood and urine as well as other measures of renal function. No other consistent defect in renal function could be demonstrated.

The inability to produce a hypertonic urine during an infusion of vasopressin seemed to rule out diabetes insipidus per se. This was confirmed by his response to the intravenous administration of 5% (hypertonic) sodium chloride solution and to the inhalation of four cigarettes (nicotine test)[2]

TABLE 2.—*Chemical Values in Urine and Serum*

	Blood	Urine
Sodium	138–142 mEq/L.	28 mEq/24 hr.*
Potassium	4.6–5.3 mEq/L.	26–70 mEq/24 hr.
Chloride	97–99 mEq/L.	25 mEq/24 hr.*
CO_2 content	23–26 mEq/L.	
Creatinine	0.85–1.02 mg. %	1.2–1.5 gm/24 hr.
B. U. N.	12–17 mg. %	
Sugar (true hexose)	50–70 mg. %	Qualitative=negative Quantitative < 1 Gm/24 hrs.
Calcium	10.1–10.7 mg. %	150–170 mg/24 hr. †
Phosphorus	4.1–4.9 mg. %	350–400 mg/24 hr. †
α-amino nitrogen		0.142–0.147 gm/24 hr.
Titratable acid		30 mEq/24 hr. †
Ammonia		80 mEq/24 hr. †
P. S. P. excretion		25% in 15 min.; 60% in 2 hr.
Creatinine clearance		110–150 cc/min.
Inulin clearance		117 cc/min.

* After a 3-day period of salt intake of approximately 500 mg. daily.
† After the administration of 10 gm. of ammonium chloride for a 2-day period.

during a sustained maximal water diuresis (Figure and Table 3). These tests indicated that his neurohypophyseal system was able to release antidiuretic hormone when stimulated by nicotine or hyperosmolality (5% sodium chloride). Conversely, when a hypotonic state or overhydration was acutely produced by a sustained positive water load of 1000 cc., the release of antidiuretic hormone was promptly inhibited and a perfectly normal water diuresis ensued (Table 4).

It was apparent from the studies described above that the only demonstrable renal defect was the inability to form a hypertonic urine. In view of previous studies,[1] it seemed possible that this might represent a reversible tubular "lesion" secondary to the prolonged polydipsia. To evaluate this possibility, it was necessary to restrict the patient's fluid intake to a level commensurate with mild but continuous dehydration. This was maintained for 20 days by rigidly restricting fluid intake to 1500 to 2500 cc. daily. His diet contained a relatively constant quantity of protein and

TABLE 3.—*Effect of Cigarette Smoking on Urinary Volume and Concentration*

Period	Vol., Cc/30 Min.	Osmolality, mOsm/L.
1	500	50
2	500	60
3	400	60
4 *	300	80
5	200	120
6	150	160
7	250	100
8	320	65

* 4 cigarettes rapidly inhaled during this period. Unfortunately a parenteral preparation of nicotine was not available for this test.

salt during this period. At the end of this period, fluid was completely restricted for 20 hours, and an infusion of vasopressin (200 milliunits per hour) was maintained for an additional 5 hours. After the maximal specific gravity and urinary osmolality had been determined (first hour of vasopressin infusion), a solution of 10% Mannitol was infused for the remaining four hours at a rate of 25 cc. per minute until an osmotic diuresis of approximately 30 cc. per minute had been attained. It was therefore possible to determine the maximal osmolality at low urinary flows and the maximal rate of water reabsorption without solute, (TmC_{H_2O}; see Comment), at very high rates of flow. The results of this last study are presented in Table 5.

The 20 days of enforced fluid restriction lead to a significant improvement in the patient's maximal concentrating ability (to 655 mOsm. per liter, specific gravity 1.025). The TmC_{H_2O} at the end of the study was slightly less than one-half the average reported normal rate (5 to 7 cc. per minute).[3] Unfortunately, because of the patient's resistance, it was not possible to continue the water deprivation further, but there seemed little question that he had an isolated reversible tubular defect.

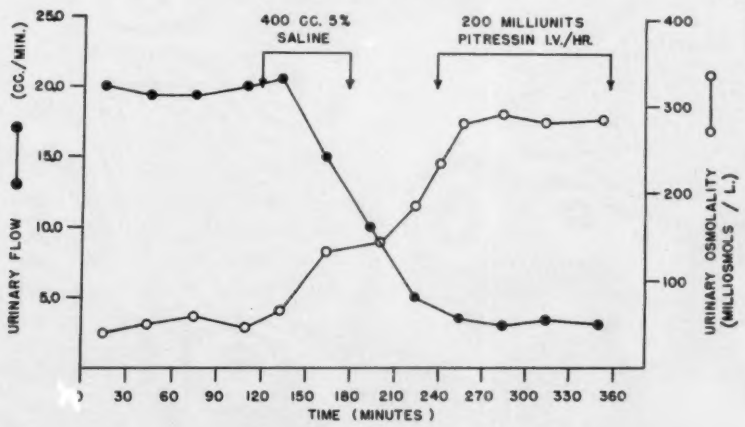


TABLE 4.—*The Maximal Diuretic Response to a Sustained Water Load* *

Rate, Cc/Min.	Minimal Osm., mOsm/L.	C_{H_2O}, Cc/Min.†	G. F. R., Cc/Min.‡	$\frac{C_{H_2O}}{G.\ F.\ R.} \times 100$
16.8	48 (Sp. gr. 1.001)	13.4	117	11.4

* These figures represent the mean of 6 consecutive 20-minute clearance periods at the height of the water diuresis.
† C_{H_2O} indicates free water clearance or the volume of urinary water virtually freed of solute during the diluting process. See comment.
‡ Glomerular filtration rate (inulin clearance).

TABLE 5.—*Maximal Urinary Osmolality and TmC_{H_2O} During Continuous Vasopressin Infusion in the Hydropenic State*

Rate, Cc/Min.	Max. Ur. Osm., mOs/L.	TmC_{H_2O}/ Cc/Min.	Creat. Clear. (G. F. R.), Cc/Min.	TmC_{H_2O}/ G. F. R. ×100
0.73	655 (Sp. Gr. 1.025)			
30.0 *	336 *	2.4 *	116 *	2.1 *

* These figures represent the mean of 5 consecutive 20-minute clearance periods.

Comment

Before discussing the probable site of the tubular lesion in the present case and its correction by water restriction, it seems appropriate to review the present concepts of the factors controlling water reabsorption by the renal tubule. These have recently been reviewed by Welt in an admirable and critical fashion, and the reader is referred to his article for a more extensive bibliography.[4]

If all the urinary water is derived from the glomerular filtrate, urine volume will vary inversely with the amount of filtered water reabsorbed. On the basis of current knowledge, the reabsorptive processes for water can be divided into three anatomic and functional phases.

In the proximal tubule, the initial phase is considered to be a passive process in which the proximal tubular fluid, made hypotonic by the *active* reabsorption of solutes, diffuses back into the blood stream along the established gradient. Therefore, the amount of *isosmotic* fluid delivered into the distal tubule is dependent upon the glomerular filtration rate and the amount of solute reabsorbed in the proximal segment. This latter process has been termed by Smith obligatory water reabsorption, and it ordinarily approximates 85% of the glomerular filtrate. That is, for every 100 cc. filtered, 15 cc. of an isosmotic fluid is delivered into the distal tubule.

In the distant segment (second phase), the reabsorption of water is dependent upon the presence of antidiuretic hormone (ADH), while solute reabsorption continues as an active process as in the proximal tubule. In the absence of ADH, little or no water is reabsorbed in this segment, and the most dilute tubular fluid is created; this is the situation seen during normal water diuresis and in diabetes insipidus. In the presence of ADH, variable amounts of water will be reabsorbed, producing a hypo- or isosmotic fluid, depending on the degree of ADH activity. As a consequence of this second phase of reabsorption, the fluid delivered into the "ultimate" or most distal segment may be of minimal osmolality and at the same volume as that delivered from the proximal tubule or it may decrease to the smallest volume necessary to excrete the urinary solutes in isotonic or isosmotic concentration.

In the "ultimate" segment (possibly the collecting tubule), water is continuously being reabsorbed *without* solutes. The amount of fluid reabsorbed during this third phase has two limiting factors; (1) the maximal urine-plasma ratio, or maximal osmotic level to which the urine can be concentrated above that of the plasma (about 1400 mOsm. per liter) and (2) the maximal rate at which fluid can be reabsorbed in this segment (5 to 7 cc. per minute per 100 cc. of glomerular filtrate).[3] This rate-limiting operation has been referred to by Homer Smith and his associates as TmC_{H_2O}.[5] Recent evidence suggests that this third or final phase of water reabsorption operates independently of ADH [6,7] and is the only mechanism for forming a hypertonic urine (one more concentrated than the plasma). Although other possibilities exist, the concept for the tubular reabsorption of water as presented

above is supported by data from a large variety of sources.[4-8] Within the framework of this formulation, Smith and his associates[5] have divided urinary water into two moieties or clearances referred to as osmolar and free water.

$V = C_{osm} + C_{H_2O}$

where

V=urinary volume
C_{osm}=osmolar clearance
C_{H_2O}=free water clearance

The osmolar clearance (C_{osm}) is the volume of fluid necessary to excrete all the urinary solutes in an isosmotic solution. This would include the solutes remaining after both proximal and distal reabsorption. It is calculated

U_{osm}=urinary osmolarity
P_{osm}=plasma osmolarity

$$C_{osm} = \text{(cc/min.)} = \frac{U_{osm}}{P_{osm}} \cdot V \text{ (cc/min.)}$$

It is apparent, therefore, that the other moiety (C_{H_2O}) or free water clearance will have a negative value when the urine is hypertonic or concentrated and a positive value when the urine is hypotonic or dilute. Expressed another way, the positive value of the free water clearance is that quantity of water delivered to the distal tubule which is virtually freed of solute during the process of urinary dilution.

An example of the calculation of osmolar clearance and positive and negative free water clearance will assist in clarifying these terms. If 15 cc. of isotonic fluid were delivered into the distal tubule and if during maximal ADH activity 90% of the solute and water were reabsorbed, 1.5 cc. of isosmotic fluid would be delivered to the TmC_{H_2O} or concentrating site. Here, fluid would be withdrawn until 0.3 cc. of a maximally concentrated urine of 1400 mOsm. per liter was formed. If we assume plasma osmolality to be 285 mOsm. per liter, then

$$C_{osm} = \frac{(1400)(0.3)}{285} = 1.5 \text{ cc. per minute}$$

and the negative

$C_{H_2O} = 1.5 - 0.3 = 1.2$ cc. per minute

Conversely, if the original 15 cc. of isosmotic fluid were delivered into the distal tubule in the absence of antidiuretic hormone, 90% of the solute would be reabsorbed without water, and 15 cc. of a very dilute fluid (osmolality 28.5 mOsm. per liter) would be delivered into the final segment. Here 5 cc. of fluid would be removed (TmC_{H_2O}), leaving 10 cc. of urine with a final concentration of 38 mOsm. per liter. Again

$$C_{osm} = \frac{(38)(10)}{285} = 1.5 \text{ cc. per minute}$$

and the positive

$C_{H_2O} = 10.0 - 1.5 = 8.5$ cc. per minute

In the present case, during maximal water diuresis a urine with a minimal osmolality of 48 mOsm. per liter was formed and a C_{H_2O} per 100 cc. of glomerular filtrate of 11.4 cc. per minute was attained (Table 4). These imply a perfectly normal diluting mechanism able to respond to the *absence* of ADH. In contrast, the initial inability to produce a urine of greater than isosmotic concentration after maximal ADH stimulation and the subsequent increase to 655 mOsm. per liter suggested an isolated defect of water reabsorption in the final tubular segment. The TmC_{H_2O} per 100 cc. of glomerular filtrate of 2.1 cc. per minute observed at the end of the study (Table 5) was less than one-half of that normally attained.[3]

It seems most apparent that the single reversible defect in the present case was secondary to the prolonged period of excessive water ingestion and the continual formation of a hypotonic urine.† This interpretation is strengthened by the recent studies of Epstein, Kleeman, and Hendrikx,[1] who observed that three days of excessive continuous fluid ingestion in normal subjects decreased both the maximal U/P osmotic ratio *and* the maximal negative free water clearance or TmC_{H_2O} attained during exposure to ADH.

† Recently, de Wardener and del Greco observed a case very similar to the present one.[9] Their patient, a long-standing psychogenic polydipsiac, was initially unable to concentrate her urine above the osmolality of her plasma. After 7 to 10 days of severe enforced dehydration, a urinary osmolality of greater than 800 mOsm. per liter was attained.

It would appear that the present case should now be added to the list of polyuric syndromes (Table 1) demonstrating an impaired response to antidiuretic hormone.‡

Summary and Conclusions

A case of psychogenic polydipsia is observed in which an isolated defect in concentrating ability was demonstrated. The investigations suggest (1) that this defect was secondary to the prolonged polydipsia, (2) that it was reversible after enforced dehydration, and (3) that it involved the "ultimate" or terminal segment of the renal tubule.

Miss M. R. Twiss, Mr. S. Krinsky, Mr. J. Yamashita, Miss W. Grant, and Miss E. Radler provided technical assistance.

Veterans' Administration Center, Wilshire & Sawtelle Blvds. (25).

‡ In unpublished observations, we have noted that some subjects with long-standing diabetes insipidus are unable to form a maximally concentrated urine when *initially* exposed to ADH. After some weeks of continuous therapy with vasopressin, this defect improves markedly. These patients may in some way be analogous to the present subject in that they also represent a reversible form of concentrating defect, probably in the ADH *dependent* site.

REFERENCES

1. Epstein, F. H.; Kleeman, C. R., and Hendrikx, A.: The Influence of Bodily Hydration on the Renal Concentrating Process, J. Clin. Invest. 36: 629-633, 1957.

2. Cates, J. E., and Garrod, O.: The Effect of Nicotine on Urinary Flow in Diabetes Insipidus, Clin. Sc. 10:145-160, 1951.

3. Zak, G. A.; Brun, C., and Smith, H. W.: The Mechanism of Formation of Osmotically Concentrated Urine During the Antidiuretic State, J. Clin. Invest. 33:1064-1074, 1954.

4. Welt, L. G.: The Influence of Disease on the Renal Excretion of Water, Yale J. Biol. & Med. 29:299-311, 1957.

5. Smith, H. W.: The Kidney: Structure and Function in Health and Disease, New York, Oxford University Press, 1951.

6. Berliner, R. W., and Davidson, D. G.: Production of a Hypertonic Urine in the Absence of Pituitary Antidiuretic Hormone, J. Clin. Invest. 35:690, 1956.

7. Kleeman, C. R.; Maxwell, M. H., and Rockney, R.: Production of Hypertonic Urine in Humans in the Probable Absence of Antidiuretic Hormone (ADH), Proc. Soc. Exper. Biol. & Med., to be published.

8. Wirz, H.: Location of Antidiuretic Action in the Mammalian Kidney by Micropuncture, in Proceedings of 20th International Physiological Congress, edited by H. Keller, New York, Academic Press, Inc., 1956, p. 972.

9. de Wardener, H. E., and del Greco, F.: Personal communication to the authors.

The Effects of Induced Hypocalcemia on Myocardial Irritability and Conductivity

The Use of Disodium Ethylenediaminetetraacetate, with Special Reference to Potassium Depletion, Digitalis Intoxication, and Digitalis-Induced Electrocardiographic Contour Changes

BERNARD KABAKOW, M.D., and MILTON J. BROTHERS, M.D., New York

The role of calcium and potassium in myocardial irritability and contractility has been well studied. More recently the interrelationship between these ions and digitalis has been explored.

The concept of synergism between, or additive effect of, calcium and digitalis has been debated for many years.[1-4] The use of potassium salts orally and parenterally in the treatment of digitalis intoxication is well established.[5,6] It is known, in addition, that low serum calcium levels potentiate the cardiac toxicity of hyperkalemia.[7]

Digitalis is known to cause egress of potassium from the myocardial cell.[8] It is this relative intracellular potassium depletion which may, in part, be responsible for the commonly observed electrocardiographic effects of digitalis.[9] Calcium ions at the cell membrane exert a stabilizing influence, making more difficult the active reentry of potassium.[10] This results in the same net effect. It seemed reasonable to expect that lowering the concentration of calcium ions at the cell membrane might facilitate entry of potassium back into the cell.

The following study was undertaken primarily to ascertain whether the commonly observed electrocardiographic manifestations of digitalis, varying from ST and T changes to evidence of marked myocardial hyperirritability, could be influenced by an induced transient hypocalcemic state.

Submitted for publication Nov. 27, 1957.

From the Division of Medicine, the Montefiore Hospital, Bronx, New York. Assistant Resident, Medical Division (Dr. Kabakow); Chief Resident, Medical Division (Dr. Brothers).

Materials and Methods

The chelating agent disodium ethylenediaminetetraacetate (Na_2 EDTA) was employed in this study to produce a transient hypocalcemia. This agent binds the available systemic calcium which is excreted in the urine as the calcium chelate. The duration and extent of the effective hypocalcemia is a function of the quantity and rapidity of administration of the Na_2 EDTA, the route of administration, and the ability of the calcium stores of the subject to replace the chelated calcium.

Twenty-six patients received a total of 27 intravenous infusions of 4 gm. of Na_2 EDTA in 250 cc. of 5% dextrose and water over a four-hour period. Electrocardiograms were taken prior to the infusions and after one, two, three, and four hours. In most cases, venous blood was drawn prior to and after the infusion and analyzed for calcium and potassium. The serum calcium was determined by the Kramer-Tisdall method,[11] and the potassium, by the use of the Beckman Model 1400 Flame Photometer.

The deviation of the ST segment is expressed in millimeters above or below the T-P segment (isoelectric line), where the latter is at the same horizontal level for two or more successive cycles and where no artifacts are present in the QRST complex. Amplitude of T waves is expressed in millimeters measured from the top of the isoelectric line to the summit of an upright T or from the bottom to the nadir of an inverted T.

Twenty patients demonstrated cardiac arrythmias suggestive of altered myocardial excitability. Five patients, three of whom were taking maintenance doses of a digitalis preparation, demonstrated marked ST depressions and T-wave inversions. One patient had no evidence of myocardial disease and was not receiving digitalis.

TABLE 1.—*The Influence of*

Patient	Sex	Age, Yr.	Diagnosis*	Daily Digitalis, Mg.	Oral K Salts	Appetite	Diuretics	Before	
								Ser. Ca, Mg. %	Ser. K, mEq/L.
1	F	66	Parkinsonism, perforated duodenal ulcer	None	None	Very poor	None	--	--
2	F	50	RHD; MS; MI; AS; AI; A. Fib.; CHF, Class IV-D	Digoxin 0.5	None	Poor	Merc. 2/wk.	--	--
3	M	71	ASHD; old myocardial infarct CHF, Class III-B	Digoxin 0.5	None	Poor	None	10.2	3.9
4	F	50	RHD; MS; MI; A. Fib.; CHF, Class IV-E	Acetyl digitoxin	None	Poor	Merc. 2/wk. NH_4Cl	10.2	4.4
5	F	65	RHD; MS; MI; A. Fib.; CHF, Class III-C	Digoxin 0.5	90 mEq/day	Fair	Merc. 1/wk.	11.0	6.35
6	M	76	ASHD; old myocardial infarct; CHF, Class IV-D	Digoxin 0.5	None	Very poor	Merc. 2/wk.	10.0	3.9
7	M	42	RHD; MS; MI; A. Fib.; CHF, Class III-C	Digoxin 0.5	None	Poor	Merc. 1/wk.	10.3	4.4
8	F	65	HCVD; A. Fib.; CHF, Class IV-E	Digoxin 0.25	None	Poor	Merc. 1/wk.	11.0	--
9	M	68	ASHD; old myocardial infarct; A. Fib.; CHF, Class III-D	Digoxin 0.5	None	Very poor	Merc. 2/wk.	--	--
10	F	80	HCVD; A. Fib.; CHF, Class III-C	Digoxin 0.25	None	Poor	Merc. 1/wk. NH_4Cl	--	--
11	M	58	RHD; MS; MI; A. Fib.; CHF, Class III-C	Digitoxin 0.1	None	Fair	Merc. 1/wk.	9.8	4.6

* RHD indicates rheumatic heart disease; MS, metral stenosis; MI, metral stenosis; AS, aortic stenosis; AI, aortic insufficiency; A. Fib., atrial fibrillation; CHF, congestive heart failure; HCVD, hypertensive cardiovascular disease; ASHD, atherosclerotic heart disease.

Results

In 11 of the 20 patients showing evidence of altered myocardial excitability, the infusion of Na_2 EDTA resulted in a marked decrease or complete disappearance of electrocardiographic signs of myocardial hyperirritability. These patients are presented in Table 1. As can be seen, with the exception of Patient 1, all patients were receiving maintenance doses of a digitalis preparation. With the exception of Patient 5, none had received supplementary potassium salts; indeed, all had clinical histories compatible with long-standing potassium depletion.

The control electrocardiograms of eight showed atrial fibrillation with multifocal premature ventricular contractions; two showed regular sinus rhythm with frequent ventricular premature contractions, and one showed complete heart block with multifocal premature ventricular contractions

TABLE 2.—*The Influence of Na_2 EDTA on*

Patient	Sex	Age, Yr.	Diagnosis	Daily Digitalis, Mg.	Oral K Salts	Appetite	Diuretics	Before	
								Ser. Ca, Mg. %	Ser. K, mEq/L.
12	M	19	RHD; MS; MI; AS; AI; A. Fib.; CHF, Class III-D	Digoxin 0.5	None	Good	Merc. 1/wk.	--	4.2
13	F	67	Amyotrophic lateral sclerosis; ASHD; CHF, Class II-B	None	None	Fair	Merc. 1/wk.	11.2	3.8
14	M	70	HCVD; pulm. fibrosis; emphysema; cor pulmonale, Class IV-D	Dig. leaf 0.1 gm.	None	Poor	Merc. 1/wk.	11.5 11.0	4.1 3.9
15	F	72	ASHD; old myocardial infarct; CHF, Class II-B	Digoxin 0.5	120 mEq. daily	Good	Merc. 1/wk.	10.1	4.5
16	F	68	ASHD, old & recent myocardial infarct; CHF, Class IV-E	Digoxin 0.25	None	Fair	Merc. 2/wk.	--	--
17	M	70	ASHD; old myocardial infarct; CHF, Class III-C	Digoxin 0.5	None	Fair	Merc. 2/wk.	10.5	5.4
18	F	69	HCVD; old myocardial infarct, CHF, Class III-D	Digoxin 0.5	None	Fair	Merc. 1/wk.	9.5	3.7
19	M	70	ASHD; complete heart block, Class II-B	None	None	Fair	None	9.5	4.3
20	M	62	HCVD; ASHD; CHF, Class III-C	Digoxin 0.25 (none in 10 days)	None	Good	Merc. 1/wk.	--	4.0

* See footnotes to Table 1 for explanations of abbreviations.

Na_2 EDTA on Ectopic Rhythms

Na_2EDTA			After Na_2EDTA	
Electrocardiogram †	Ser. Ca, Mg. %	Ser. K, mEq/L.	Electrocardiogram †	Remarks †
RSR with fixed coupling	--	--	RSR	Pt. given initial I. V. and then oral potassium with no recurrence of arrhythmia
Atrial fibrillation with coupling	--	--	Atrial fibrillation, no v. p. c.'s	V. p. c.'s returned in 12 hr.; potassium started with abolition of v. p. c.'s in 48 hr.
Complete heart block, coupling, & multifocal v. p. c.'s	9.1	4.3	Complete heart block, no v. p. c.'s	Oral potassium started; digitalis stopped for 48 hr. then resumed with no further v. p. c.'s
Atrial fibrillation, multifocal v. p. c.'s, & coupling	7.6	3.7	Atrial fibrillation, no v. p. c.'s	Pt. given oral potassium supplements
Atrial fibrillation & bigeminy	8.1	5.7	Atrial fibrillation, very few v. p. c. 's	V. p. c.'s returned; pt. given I. v. K with decrease of v. p. c.'s in 48 hr.
RSR with frequent multifocal v. p. c.'s	8.9	4.4	RSR with occasional v. p. c.'s	Pt. given oral K with no return of multifocal v. p. c.'s
Atrial fibrillation with frequent multifocal v. p. c.'s	8.1	4.2	Atrial fibrillation with occasional v. p. c.'s	Pt. given oral K, then digitalis resumed with no return of v. p. c.'s
Atrial flutter; fib. with multifocal v. p. c.'s	10.0	--	Atrial flutter; fib.; no v. p. c.'s	V. p. c.'s returned; pt. could not tolerate oral K; I. V. K given with decrease of v. p. c.'s in 24 hr.
Atrial fibrillation; multifocal v. p. c.'s	--	--	Atrial fibrillation; no v. p. c.'s	Given oral K; digitalis resumed in 24 hr. with no return of v. p. c.'s
Atrial fibrillation with frequent v. p. c.'s	--	--	Atrial fibrillation; no v. p. c.'s	Pt. given oral K with no return of v. p. c.'s
Atrial fibrillation with frequent v. p. c.'s	8.5	4.9	Atrial fibrillation; few v. p. c.'s	Pt. given oral K & digitalis continued without increase in v. p. c.'s

† V. P. C., indicates ventricular premature contractions.

and coupling. The responses to the Na_2 EDTA infusion, in the following three of these cases, are illustrated in Figure 1, Patient 1 was the only one of this group who had received no digitalis. This patient had daily vomiting and a negligible food intake for two weeks prior to this study. Roentgenograms revealed free air under the diaphragm. The patient was surgically explored and a perforated duodenal ulcer found. After the response to the Na_2 EDTA infusion, given preoperatively, the patient was given potassium parenterally and then maintained with adequate oral potassium intake. During a one-month follow-up there had been no recurrence of the arrhythmia.

Patient 2, who had rheumatic heart disease, and demonstrated atrial fibrillation with fixed coupling, was given maintenance digitalis, had a low potassium intake, and received frequent mercurial diuretics. The

*Ectopic Rhythms and Conduction Disturbances**

Na_2EDTA			After Na_2EDTA	
Electrocardiogram	Ser. Ca, Mg. %	Ser. K, mEq/L.	Electrocardiogram	Remarks
Atrial fibrillation with v. p. c.'s	--	4.3	No change	Patient had v. p. c.'s prior to digitalis; no response to oral potassium
RSR with bigeminy	8.7	3.3	No change	Pt. had this ectopic rhythm while in CHF and not given digitalis; no response to I. V. K; digitalization caused decrease in v. p. c.'s
Atrial fibrillation with frequent v. p. c.'s	9.5 9.4	4.0 3.3	No change	No response to I. V. K or oral quinidine; O_2 and respirator caused reversion to RSR; no v. p. c.'s
RSR with trigeminy	8.5	3.7	No change	Ectopic rhythm abolished with oral quinidine
Supraventricular tachycardia	--	--	No change	No response to I. V. K; at p. m. fresh post. wall myocardial infarct found
Atrial flutter with a 2:1 block	9.0	5.9	No change	4:1 block with carotid sinus massage; pt. maintained with digitalis
1st degree heart block with few v. p. c.'s	6.7	2.9	No change	At p. m. 3 mo. later, heart showed marked myocardial scarring
Complete heart block	7.7	3.9	No change	At p. m. there was extensive calcification of intervent. septum & bundle of His
RSR, multifocal v. p. c.'s; runs of bigeminy	--	3.9	No change	No response to oral potassium

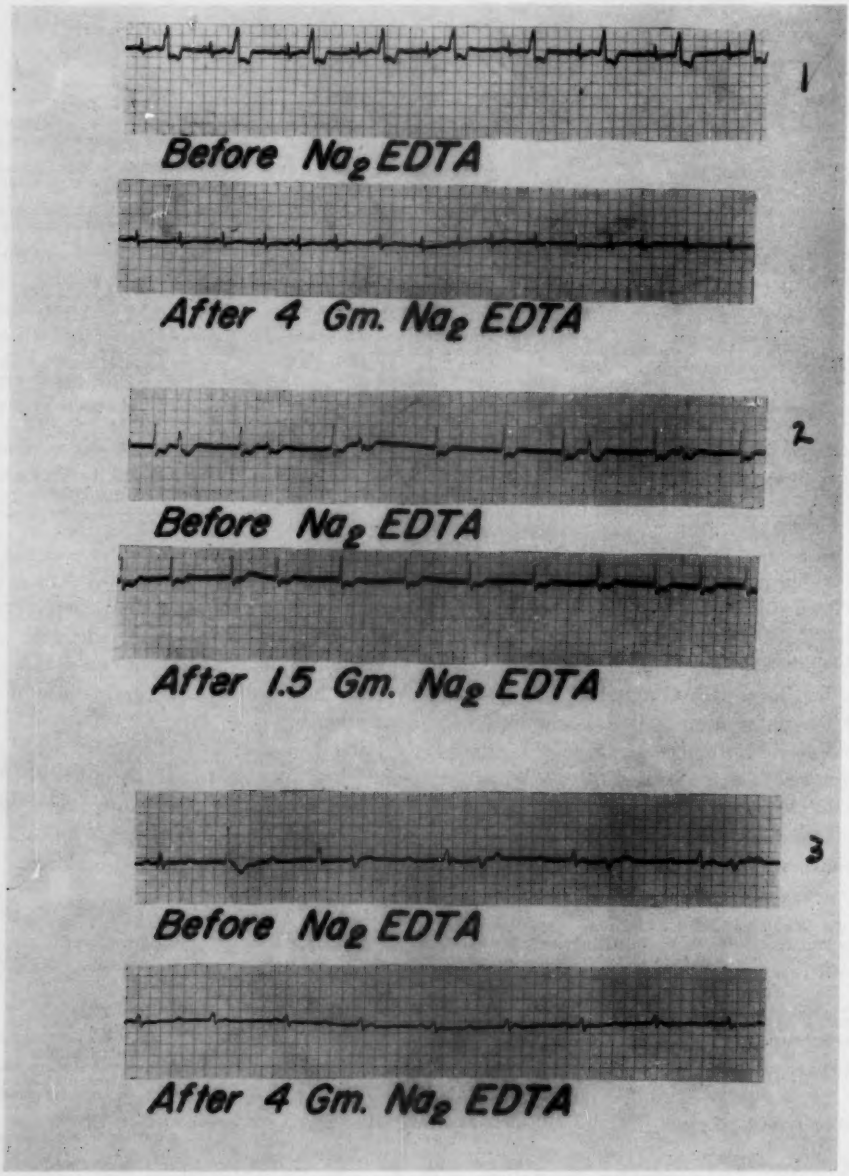


Fig. 1.—Electrocardiograms (Lead II) of three patients responding to the Na_2 EDTA infusion. All three patients were potassium-depleted, and two of them, Patients 2 and 3, were taking maintenance digitalis. It is to be noted that Patient 2 had complete abolition of the ectopic beats after only 1.5 gm. of Na_2 EDTA.

infusion of Na_2 EDTA resulted in complete abolition of the ventricular premature contractions. Digitalis was withheld, and the patient was given no supplementary potassium until 24 hours after the test procedure, by which time the premature contractions had returned. Oral potassium, instituted at this time, resulted in the disappearance of the ectopic rhythm after two days.

TABLE 3.—*The Influence of Na_2 EDTA and Edathamil Calcium-Disodium on the*

Patient	Sex	Age, Yr.	Diagnosis	Daily Digitalis, Mg.	Chelating Agent	ECG Segment *	I
21	M	50	Hypertensive cardiovascular disease	Digitoxin 0.1	Na_2EDTA	T_b	−0.75
						T_a	−2.5
						ST_b	0
						ST_a	0
22	F	33	Rheumatic heart disease	Digoxin 0.5	Na_2EDTA	T_b	+2.5
						T_a	+2.5
						ST_b	−1.5
						ST_a	−1
23	M	66	Hypertensive cardiovascular disease	Digoxin 0.25	Na_2EDTA	T_b	−2.5
						T_a	−2.75
						ST_b	−1.5
						ST_a	−0.75
			Hypertensive cardiovascular disease	Digoxin 0.25	Edathamil calcium-disodium	T_b	+1
						T_a	+0.75
						ST_b	−1
						ST_a	−1
24	F	72	Arteriosclerotic cardiovascular disease; angina pectoris	None	Na_2EDTA	T_b	−1
						T_a	−1
						ST_b	0
						ST_a	0
25	M	56	Arteriosclerotic cardiovascular disease; angina pectoris	None	Na_2EDTA	T_b	−0.5
						T_a	−0.5
						ST_b	−0.5
						ST_a	0
26	F	50	Metastatic carcinoma (no heart disease)	None	Na_2EDTA	T_b	+1.25
						T_a	+1.25
						ST_b	0
						ST_a	0

* T_b indicates T wave before chelating agent; T_a, T wave after chelating agent; ST_b, ST segment before chelating agent; ST_a, ST segment after chelating agent.
† Numbers refer to millimeters above (+) or below (−) isoelectric line.

Patient 3, who had arteriosclerotic cardiovascular disease and had sustained a posterior wall myocardial infarction five years previously, had an electrocardiogram which showed complete heart block, present since the infarction, and multifocal premature ventricular contractions. This patient was anorexic, had received no potassium salts, and was taking maintenance digoxin. After the abolition of premature systoles by Na_2 EDTA, he was given potassium orally, and 48 hours later digitalis was reinstituted without the reappearance of the ectopic rhythm.

The remaining nine patients manifesting electrocardiographic evidence of altered myocardial irritability, but not responding to Na_2 EDTA, are listed in Table 2. All of these patients except Patients 13 and 19 were taking maintenance digitalis. Of the seven patients taking digitalis, the electrocardiograms of six could be interpreted as showing ventricular hyperirritability, that of the seventh, Patient 17, showing atrial flutter with a 2:1 block. The remaining two patients, Patients 13 and 19, had received no digitalis for many months, and their electrocardiograms demonstrated bigeminy and complete heart block, respectively. The infusion of Na_2 EDTA did not influence the rhythm in any of this group of nine patients. Although only one of these patients, Patient 15, was taking supplementary potassium, the diets of all, except Patient 14, were considered to be adequate. All, except Patient 19, had received mercurial diuretics with varying frequency. Patient 12, whose dietary intake was excellent, had shown premature contractions before he was digitalized. This patient did not respond to oral potassium and, because of increasing cardiac decompensation, digitalis was continued without worsening of the ectopic rhythm. Patient

Electrocardiograms of Digitalized and Nondigitalized Patients

Leads †											Relative Q–T Duration	
II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6	Before	After
−0.5 −1.2	0 −0.25	+1 +1.75	−0.5 −1.25	−0.75 −0.5	+3 +5	+6 +9	+4.75 +5.25	+2.25 0	−1.5 −2.25	−2 −2.75	1.15	1.32
+0.5 +0.5	+0.5 +0.5	+0.25 +0.25	0 0	+0.25 +0.25	−0.5 −0.25	−1.5 −0.25	−2.25 −0.5	−2.0 −0.5	0 0	+1 +1		
−2.5 −1.5	−3.5 −2	−2.5 −1	+2.75 +2.5	−3.5 −1.5	−3.5 −2.5	−6 −5.5	−5 −4.5	−3 −5	−2 −2	+2.5 +2.5	0.89	1.14
−1.5 −0.5	−1 −0.5	+1 +1	−0.5 0	0 0	0 0	−3 −2	−4 −1.5	−3 −1.5	−2 −1.75	−0.5 −0.5		
+2.5 +0.5	+5.5 +2	+1.75 +1.25	−4 −2	+3.5 +0.75	0 0	0 +3.5	+3 +2	−6 −3	+1.5 0	+3.5 +2.25	1.58	1.60
−0.5 −0.5	0 +0.25	+0.5 +0.5	0 0	0 0	+3.5 +2.25	+3.5 +2	+1.5 +1	−5 −0.75	−3.5 −1	−3 −0.5		
+2.5 0	+3.5 +0.75	−0.5 0	+0.5 +0.5	+2 0	0 0	+2 0	+4.5 +5.5	−7 −6.5	+1 +0.5	+3.5 +3	1.11	1.16
0 0	+0.5 +0.5	+0.5 +0.5	−0.5 −0.5	0 0	+1.5 +2	+1.5 +2	+1.5 +1.5	−4.5 −4.5	−3.5 −3	−3.5 −3		
−1 −0.75	−0.5 −0.5	+1 +1	−0.5 −0.5	−1 −1	+1 +1	+1 +1	−4 −4	−6 −7	−3.5 −4.5	−1.75 −2.25	0.95	1.12
0 0	0 0	+0.5 +0.5	0 0	−0.75 −0.5	+0.5 0	0 0	−1.5 −1	−1 −1	−1 −1	−1 −1		
+0.25 0	−0.5 +0.5	+0.25 +0.75	−0.5 −0.5	+0.25 +0.25	+2 +2	+1 +0.5	−1 −0.5	−1.5 −2.5	−1 −1.5	−1 −1.25	1.12	1.25
0 0	0 0	+0.5 0	0 0	0 0	+0.5 +0.5	+2 +3	+1.25 +1	−1 −1	−2 −2	−1.5 −1.5		
+2 +2	+1.25 +0.5	−1.5 −1	0 +1	+2 +1.25	−1 −0.25	−1.5 +0.5	0 +0.5	0 +1	+1 +1.5	+1.5 +2	1.13	1.26
0 0	0 0	+1.25 0	0 0	0 0	+0.5 +0.25	−0.5 0	0 0	0 0	+0.25 0	+0.75 0		

13 had demonstrated prolonged periods of bigeminal rhythm, during episodes of congestive heart failure only. Her decompensation had been treated in the past with bed rest and mercurial diuretics with a resultant decrease in the frequency of the premature ventricular contractions. This patient had received no digitalis preparation for five months prior to the infusion of Na_2 EDTA. Upon the failure of Na_2 EDTA and intravenous potassium to affect the rhythm favorably, digitalization was accomplished, with a resultant improvement in the state of compensation and reversion of the electrocardiographic pattern to that of regular sinus rhythm with occasional premature ventricular contractions.

Patient 14 had severe pulmonary fibrosis and emphysema. He had been taking maintenance digitalis and presented with an electrocardiogram showing atrial fibrillation with frequent multifocal premature ventricular contractions. This patient received two infusions of Na_2 EDTA and also intravenous potassium without any alteration of the rhythm. When severe dyspnea and cyanosis developed, the patient was placed in a chest respirator and given oxygen. This procedure resulted in complete disappearance of all premature ventricular contractions and restoration of normal sinus rhythm.

Patient 15, with arteriosclerotic cardiovascular disease and a history of an old myocardial infarction, developed a trigeminal rhythm while taking maintenance digitalis and oral potassium salts. After failure of Na_2 EDTA to affect the arrhythmia, the patient received quinidine, with the restoration of regular sinus rhythm.

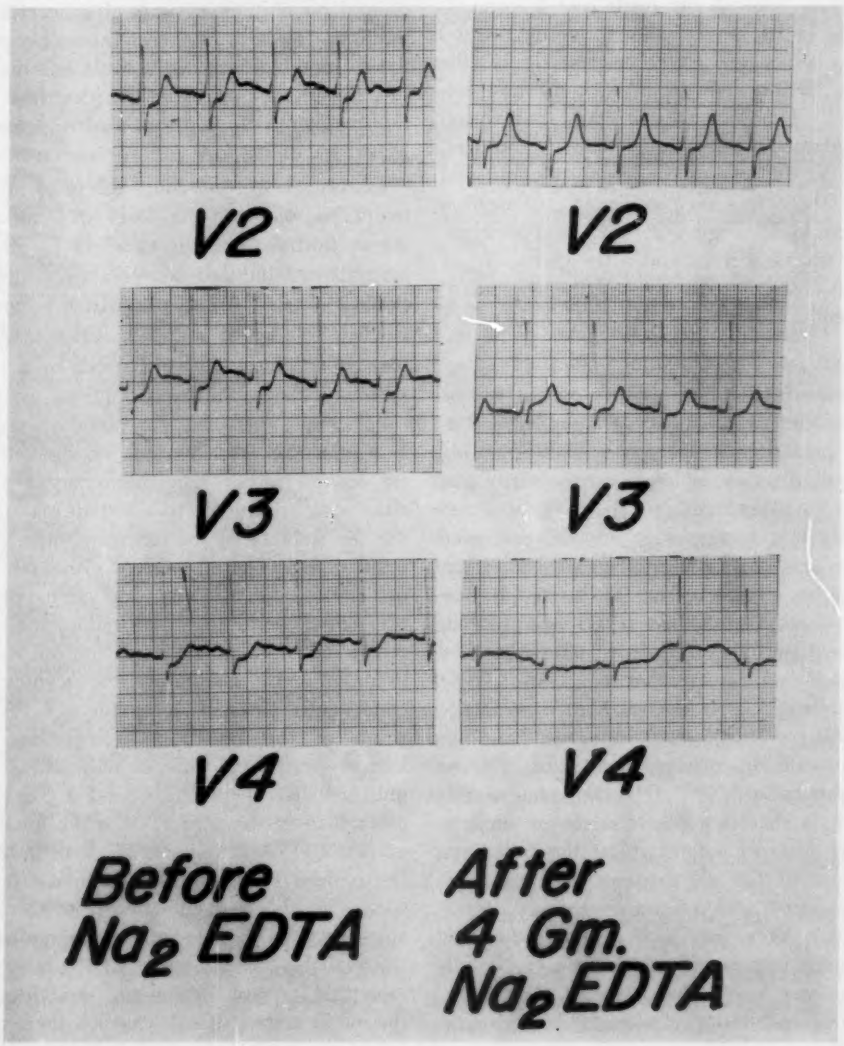
Patient 16, with arteriosclerotic cardiovascular disease, developed a rapid supraventricular tachycardia while taking maintenance digitalis. After the Na_2 EDTA infusion, intravenous potassium was

similarly unsuccessful in affecting this arrhythmia. The serum glutanic oxalactic (SGO) transaminase was elevated, and later, at postmortem examination, a fresh posterior wall myocardial infarction was found.

The supraventricular tachycardia of Patient 17 responded to carotid sinus massage, and the patient was maintained with digitalis. Two cases, Patients 18 and 19, showed evidence of severe myocardial scarring at postmortem examination.

Table 3 represents the influence of Na_2 EDTA upon the T wave, the ST segment, and the Q-T interval in the electrocardiograms of six patients. Five of these, each of whom had a history of heart disease, showed, initially, significant ST and T alterations. Patient 26 had no history of heart disease, an essentially normal electro-

Fig. 2.—Patient 21, a 50-year-old man with hypertensive cardiovascular disease, was taking daily maintenance doses of 0.1 mg. of digitoxin. It is to be noted that the U waves are markedly diminished after the Na_2 EDTA infusion.



cardiogram, and was not taking digitalis. The T waves and ST segments of the three patients taking maintenance digitalis reverted to or toward the isoelectric line under the influence of Na_2 EDTA. One of these patients, Patient 23, received, in addition, an infusion of edathamil calcium-disodium, which failed to affect these contour changes. The depressed segments of the other two patients, who had never taken digitalis but who had left ventricular hypertrophy and coronary insufficiency, were unaffected by Na_2 EDTA. As indicated in Table 3, the relative Q-T duration (Rel. Q-T), as calculated by the method of Lepeschkin,[12] was increased by the hypocalcemia induced in each of these patients. The patient receiving an infusion of edathamil calcium-disodium, of course, had no depression of serum calcium, and thus there was no significant prolongation of the Q-T. Figure 2 shows a representative tracing before and after giving 4 gm. of Na_2 EDTA to one of the digitalized patients, Patient 21.

Comment

One of the causes of myocardial hyperexcitability is a state of relative intracellular potassium depletion. The initiating stimuli for this depletion can be many and varied and include (1) disease states and therapeutic measures which cause a total body loss of potassium, such as vomiting, diarrhea, excessive use of mercurial diuretics, cation-exchange resins and adrenocortical steroids; (2) a diseased overworked heart [13-18]; (3) hypothermic states [19]; (4) digitalis.[8] There is a plethora of evidence in the literature which indicates that digitalis causes an egress of potassium from the myocardial cell.[8,20-24] The consensus of this work is that therapeutic doses of digitalis exert little or no effect on the potassium content of the myocardium, whereas toxic doses cause a significant depletion of intracellular potassium. Accordingly, ectopic rhythms associated with the use of digitalis have been successfully treated with intravenous and oral potassium.[6,25,26] More recently evidence was presented that ectopic rhythms and disturbances in A-V conduction, in patients not receiving digitalis, could be favorably influenced by the use of intravenous potassium. Conversely, ectopic rhythms may be observed in the absence of any evident cause for potassium depletion. It is in these cases that potassium is without effect.[27]

In order to affect the arrhythmia consistently with potassium in depletion states, it is usually necessary to employ a rapid intravenous infusion. Even with the use of oral potassium, in congestive heart failure,[28] the recognized narrow range between the therapeutic dose and a toxic one makes this considerably less than an ideal tool for the treatment or investigation of myocardial hyperexcitability states.

It seemed worth while therefore, to attempt to decrease the level of available serum calcium in order to affect favorably arrhythmias induced by potassium depletion. The basis for this approach is somewhat as follows: it is known that potassium passes out of the myocardial cell by a passive process of diffusion during muscle contraction. Between contractions, potassium must be carried back into the cell by an active process requiring energy. Calcium ions are known to assist in maintaining the stability of the cell membrane, thus regulating its permeability to the reentry of potassium.[7,10] The induction of a transient hypocalcemia may reduce the concentration of calcium ions at the cell membrane, thereby facilitating the reentry of endogenous potassium into the cell. As a result of the Na_2 EDTA infusion, the ionized serum calcium is reduced. It is unlikely that chelation occurs at any site other than in the serum, since the quantity of Na_2 EDTA introduced does not bind all the ionized calcium in the serum. In response to this reduction, however, and in an attempt to replenish the serum calcium, the available calcium stores of the body are mobilized.[29] Although bone, doubtless, is the major source of this calcium, there may

occur a contribution to this replenishment by other sources, including cellular and membrane calcium.

The average depression of serum calcium induced by the infusion of 4 gm. of Na_2 EDTA in our series was 1.9 mg.%. In that group of patients in which Na_2 EDTA produced an amelioration of myocardial hyperexcitability, one-half of these showed evidence of such amelioration after the infusion of 1 gm., and in most the maximum effect was demonstrated after 3 gm. The side-effects observed during the infusion of Na_2 EDTA were temporary and did not persist beyond the period of the infusion. These consisted of pain and burning at the site of the needle and along the course of the utilized vein in all patients. The patients' tolerance of this pain varied markedly, but in no instance was it necessary to discontinue the infusion. In one-third of the patients circumoral paresthesiae and a subjective sensation of facial heat were experienced. In none of the patients, however, was tetany observed or a Chvostek or Trousseau sign elicited. A slight hypotension, not exceeding 15 mm. systolic and 10 mm. diastolic, was observed in about half of the cases. The only evidence of toxicity that we have found in the literature was that reported with the use of a dose 7 to 10 times greater than that employed in this study and with repeated administration on consecutive days. In that report renal toxicity was produced in two patients, with consequent oliguria, azotemia, and a fatal outcome. Postmortem examination revealed degeneration and vacuolation in the cells of the convoluted tubules of the kidney.[30] In another report,[29] in which daily intravenous infusions of 4 gm. of Na_2 EDTA were given in a four-hour period to a large number of patients, there were no pathological findings attributable to Na_2 EDTA. In none of our cases was there any evidence of renal toxicity.

The evidence, as presented in the cases described in Table 1, strongly suggests that in the face of potassium depletion the induction of a transient hypocalcemia is an effective and rapid means of temporarily abolishing ectopic rhythms and also predicting the response to subsequent potassium supplementation. The potentially dangerous rhythm is abolished, while the body may be repleted with potassium via the oral route, obviating the need for intravenous potassium.

Table 2, which summarizes those cases not responding to Na_2 EDTA, many of whom received potassium with similarly unsuccessful results, suggests that this lack of response connotes an ectopic rhythm having its genesis in some cause other than potassium depletion. In these cases, therefore, an increase in cell-membrane permeability to the reentry of potassium through the mechanism of hypocalcemia would be without effect. In this group of patients, when indicated for the improvement of the patient's circulatory status, digitalis was safely continued.

Induced hypocalcemia, utilizing the chelating action of EDTA, has been reported previously to revert digitalis-induced arrhythmias in dogs.[7,31] More recently, three cases of spontaneously occurring digitalis intoxication in human patients were successfully treated in this manner.[32]

In the group of patients presented, in which the effect of Na_2 EDTA on ST and T contour changes was studied, the major depressions were observed in the precordial leads in both the digitalized and the nondigitalized group. This observation, a common one in clinical medicine, is explained by the fact that the digitalis pattern is produced by slowing of repolarization in the apical regions.[33] In the two patients not receiving digitalis, chamber enlargement was responsible for the ST and T depressions observed in the precordial leads.

The typical electrocardiographic pattern of potassium-depletion states such as periodic paroxysmal paralysis is, in many respects, similar to that observed with digitalis effect.[34,35] It is our contention that the reversion of the ST and T toward the

isoelectric line induced by the transient hypocalcemia in those patients receiving digitalis may represent repletion of intracellular myocardial potassium. The remaining depressions in these cases represent the contribution to the contour depressions by chamber enlargement or myocardial ischemia.

In this study, no correlation could be found between changes in serum potassium levels and response to the Na_2 EDTA infusion. This is, perhaps, in keeping with the lack of correlation between serum potassium levels and changes in intracellular potassium content.[36] Indeed, the gradient of potassium across the cell membrane may be the major factor influencing excitability, rather than the absolute concentration on either side of the membrane.

Summary and Conclusions

The effect of transient hypocalcemia induced by the use of the chelating agent disodium ethylenediamenitetraacetate (Na_2 EDTA) has been studied in 26 patients. In 11 patients the ectopic rhythms were abolished. In nine patients Na_2 EDTA had no effect upon altered myocardial irritability and conductivity. In three patients receiving digitalis and showing ST and T wave depressions, Na_2 EDTA caused a reversion toward the isoelectric line of these segments. In two patients with similar electrocardiographic changes, receiving no digitalis but with evidence of chamber enlargement or coronary insufficiency, Na_2 EDTA was without effect. In one patient with no evidence of heart disease and with a normal electrocardiogram, no effect on ST and T waves was observed. The interrelationship of digitalis, potassium, and calcium, as they affect myocardial irritability, is discussed.

It is concluded that the induction of a transient hypocalcemia in patients receiving digitalis and/or presenting evidence of myocardial hyperexcitability, may be of value in (1) evaluating the role of potassium depletion in the production of the ectopic rhythm, (2) the safe temporary abolishment of a potentially dangerous arrhythmia, during which time replenishment of potassium stores may be accomplished by the oral route, and (3) the evaluation of contour changes observed in the electrocardiograms of patients receiving digitalis.

Mr. George Ross, Dr. Joseph Samachson, and their laboratory staffs cooperated in the performance of the serum potassium and calcium determinations.

Dr. Louis Leiter, Chief, Division of Medicine of the Montefiore Hospital, gave criticism, advice, and encouragement.

Division of Medicine, Montefiore Hospital, Gun Hill Rd. near Jerome Ave. (67) (Dr. Brothers).

REFERENCES

1. Gold, H., and Edwards, D. J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, Am. Heart J. 3:45, 1927.

2. Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: Warning, with Report of 2 Deaths, J. A. M. A. 106: 1151, 1936.

3. Smith, P. K.; Winkler, A. W., and Hoff, H. E.: Calcium and Digitalis Synergism: Toxicity of Calcium Salts Injected Intravenously into Digitalized Animals, Arch. Int. Med. 64:322, 1939.

4. Salter, W. T., and Runels, E. A.: A Nomogram for Cardiac Contractility Involving Calcium, Potassium and Digitalis-like Drugs, Am. J. Physiol. 165:520, 1951.

5. Lown, B.; Weller, J. M.; Wyatt, N.; Hoigne, R., and Merrill, J. P.: Effects of Alterations of Body Potassium on Digitalis Toxicity, J. Clin. Invest. 31:648, 1952.

6. Lown, B., and Levine, S. A.: Medical Progress: Current Concepts in Digitalis Therapy, New England J. Med. 250:771, 819, and 866, 1954.

7. Page, E., and Real, J. D.: Interrelationships Between Cardiac Effects of Ouabain, Hypocalcemia and Hyperkalemia, Circulation Res. 3:501, 1955.

8. Schreiber, S. S.: Potassium and Sodium Exchange in the Working Frog Heart, Am. J. Physiol. 185:337, 1956.

9. Surawicz, B., and Lepeschkin, E.: The Electrocardiographic Pattern of Hypopotassemia With and Without Hypocalcemia, Circulation 8:801, 1953.

10. Armitage, A. K.; Burn, J. H., and Gunning, A. J.: Ventricular Fibrillation and Ion Transport, Circulation Res. 5:98, 1957.

11. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of

Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. 63:461, 1925.

12. Lepeschkin, E.: Modern Electrocardiography, Baltimore, Williams & Wilkins Company, 1951.

13. Harrison, T. R.; Pilcher, C., and Ewing, G.: Studies in Congestive Heart Failure: IV. The Potassium Content of Skeletal and Cardiac Muscle, J. Clin. Invest. 8:325, 1930.

14. Calhoun, J. A.; Cullen, G. E.; Clarke, G., and Harrison, T. R.: Studies in Congestive Heart Failure: VI. The Effect of Overwork and Other Factors on the Potassium Content of Cardiac Muscle, J. Clin. Invest. 9:393, 1931.

15. Wilkens, W. E., and Cullen, G. E.: Electrolytes in Human Tissue: III. A Comparison of Normal Hearts with Hearts Showing Congestive Heart Failure, J. Clin. Invest. 12:1063, 1933.

16. Mangun, G. H.; Reichle, M. S., and Myers, V. C.: Further Studies on Human Cardiac and Voluntary Muscle: Possible Implications of Changes in the Creatine, Phosphorus and Potassium Content, with Special Reference to Heart Disease, Arch. Int. Med. 67:320, 1941.

17. Iserli, L. T.; Alexander, L. C.; McCaughey, R.; Boyle, A. J., and Myers, G. B.: Water and Electrolyte Content of Cardiac and Skeletal Muscle in Heart Failure and Myocardial Infarction, Am. Heart J. 43:215, 1952.

18. Clarke, N. E., and Mosher, R. E.: The Water and Electrolyte Content of the Human Heart in Congestive Heart Failure With and Without Digitalization, Circulation 5:907, 1952.

19. Covino, B. G., and Hegnauer, A. H.: Electrolytes and pH Changes in Relation to Hypothermia, Circulation Res. 3:575, 1955.

20. Calhoun, J. A., and Harrison, T. R.: Studies on Congestive Heart Failure: IX. The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs, J. Clin. Invest. 10: 139, 1931.

21. Hagen, P. S.: The Effects of Digilanid C in Varying Dosage upon the Potassium and Water Content of Rabbit Heart Muscle, J. Pharmacol. & Exper. Therap. 67:50, 1939.

22. Wedd, A. M.: The Influence of Digoxin on the Potassium Content of Heart Muscle, J. Pharmacol. & Exper. Therap. 65:268, 1939.

23. Wood, E. H., and Moe, G. K.: Blood Electrolyte Changes in the Heart-Lung Preparation with Special Reference to the Effects of Cardiac Glycosides, Am. J. Physiol. 137:6, 1942.

24. Holland, W. C.; Greig, M. E., and Dunn, C. E.: Factors Affecting the Action of Lanatoside C on the Potassium Content of Isolated Perfused Guinea Pig Hearts, Am. J. Physiol. 176:227, 1954.

25. Sampson, J. J.; Alberton, E. C., and Kondo, B.: The Effect on Man of Potassium Administration in Relation to Digitalis Glycosides with Special Reference to Serum Potassium, the Electrocardiogram and Ectopic Beats, Am. Heart J. 26:164, 1943.

26. Enselberg, C. D.; Simmons, H. G., and Mintz, A. A.: The Effects of Potassium upon the Heart with Special Reference to the Possibility of Treatment of Toxic Arrhythmias Due to Digitalis, Am. Heart J. 39:713, 1950.

27. Bettinger, J. C.; Surawicz, B.; Bryfogle, J. W.; Anderson, B. N., Jr., and Bellet, S.: The Effect of Intravenous Administration of Potassium Chloride on Ectopic Rhythms, Ectopic Beats, and Disturbances in A-V Conduction, Am. J. Med. 21:521, 1956.

28. Brown, H.; Tanner, G. L., and Hecht, H. H.: The Effect of Potassium Salts in Subjects with Heart Disease, J. Lab. & Clin. Med. 37:506, 1951.

29. Spencer, H.; Greenberg, J.; Berger, E.; Perrone, M., and Laszlo, D.: Studies on the Effect of Ethylenediaminetetraacetic Acid in Hypercalcemia, J. Lab. & Clin. Med. 47:29, 1956.

30. Dudley, H. R.; Ritchie, A. C.; Schilling, A., and Baker, W. H.: Pathologic Changes Associated with the Use of Sodium Ethylene Diamine Tetraacetate in the Treatment of Hypercalcemia: Report of 2 Cases with Autopsy Findings, New England J. Med. 252:331, 1955.

31. Smith, P. W., and Grinnell, E. H.: Effect of Di-Potassium Ethylenediamine Tetraacetate on Digitalis-Produced Cardiac Arrhythmias, Fed. Proc. 14:387, 1955.

32. Gubner, R. S., and Kallman, H.: Treatment of Digitalis Toxicity by Chelation of Serum Calcium, Am. J. M. Sc. 234:136, 1957.

33. Levine, H.; Nahum, L. H.; Geller, H. M., and Sikand, R. S.: Genesis of the Electrocardiographic Pattern of Digitalis, Am. J. Physiol. 167: 726, 1951.

34. Lepeschkin, E.: Studies on the Electrocardiographic Patterns in Electrolyte Imbalance, Am. J. Physiol. 167:287, 1951.

35. van Buchem, F. S. P.: The Electrocardiogram and Potassium Metabolism: Electrocardiographic Abnormalities in Primary Aldosteronism and Familial Periodic Paralysis, Am. J. Med. 23: 376, 1957.

36. Aikawa, J. K., and Fitz, R. H.: Exchangeable Potassium Content of the Body in Congestive Heart Failure: Changes During Treatment, Circulation 14:1093, 1956.

Atypical Heat Stroke, with Hypernatremia, Acute Renal Failure, and Fulminating Potassium Intoxication

CAPT. CHARLES R. BAXTER (MC), and MAJOR PAUL E. TESCHAN (MC), U. S. Army

The criteria for the diagnosis of heat stroke are well known, but atypical clinical findings, such as abnormal behavior patterns without severe hyperpyrexia following exposure to heat, may go unrecognized.[1] Detailed chemical studies are lacking in all reported cases of heat injury. A small but definite incidence of acute renal failure occurring in the course of severe heat injury has been reported.[1,16,18] However, relatively little clinical and chemical detail has been included.

Three fatal cases of heat injury with oliguria occurring in military personnel stationed near San Antonio, Texas, are presented to (1) describe some clinical and chemical findings that may precede this atypical clinical form of heat stroke, (2) suggest means of preventing the associated acute renal failure with oliguria, and (3) account for the deaths of these patients on the basis of shock, persistent hyperthermia, and remarkably rapid rise in plasma potassium concentration with fulminating myocardial potassium intoxication.

Report of Cases

CASE 1.—In June, 1956, a 20-year-old recruit, a native of New York State, reported for training in San Antonio, Texas. He was in good health, with no antecedent history of significant disease. Upon arrival, sun helmets were issued and processing began. Ambient temperature was 103 F. Six hours after arrival the patient complained of transient dizziness, relieved by sitting down and leaning forward. The following day he complained of stabbing pains around the ears and eyes and mild blurring of vision. Early the next day, he was noted to make inappropriate remarks and fumble at routine tasks. By 6 p. m., his actions became irrational and combative, resulting in the administration of 12½ grains (0.81 gm.) of amobarbital sodium (Sodium Amytal) and admission to the psychiatric ward. Examination at this time revealed pulse, 180 per minute; blood pressure, 80/60 mm. of Hg; rectal temperature, 106 F, and respirations, 40 per minute. The patient was semicomatose, struggling intermittently, and speaking incoherently. Enophthalmos and poor skin turgor were present. Mucous membranes were dry and congested; the neck veins were flat, and the neck supple. Examination of the chest was negative except for shallow rapid respiratory movements and tachycardia. There was considerable abdominal guarding and diffuse tenderness. The extremities were cold, dry, and deeply cyanotic. Capillary filling was poor. Neurologic examination was negative except for depressed deep-tendon reflexes.

On transfer to the medical ward at 11 p. m., oxygen at 8 liters per minute by nasal catheter and alcohol sponging in an air current from an electric fan were begun; 500 cc. of dextran, 1000 cc. of lactated Ringer's injection, and 1600 cc. of dextrose in water were administered intravenously during the ensuing 10 hours without clinical improvement except that the blood pressure rose temporarily to 140/90 mm. of Hg and the pulse slowed to 120 per minute. The rectal temperature remained between 104 and 105 F for five hours, dropping transiently to 101.6 F, then remained between 102.6 and 103.8 F throughout the remaining hospital course. The blood pressure fell gradually to 100/80 mm. of Hg, while the pulse remained at 120 per minute.

By 9 a. m., the following morning, admission laboratory results were available: hemoglobin, 13.3 gm. per 100 cc.; hematocrit, 43%; WBC, 25,100 per cubic millimeter; differential count, neutrophils 92%, lymphocytes 5%, monocytes 2%; no urine was available for analysis. Lumbar puncture revealed an opening pressure of 120 mm. of water; cell count was 6 lymphocytes per cubic millimeter; sugar, 130 mg. per 100 cc.; total protein, 37 mg. per 100 cc. The results of blood chemistry studies are recorded in Figure 1.

Submitted for publication Nov. 4, 1957.

From the U. S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas.

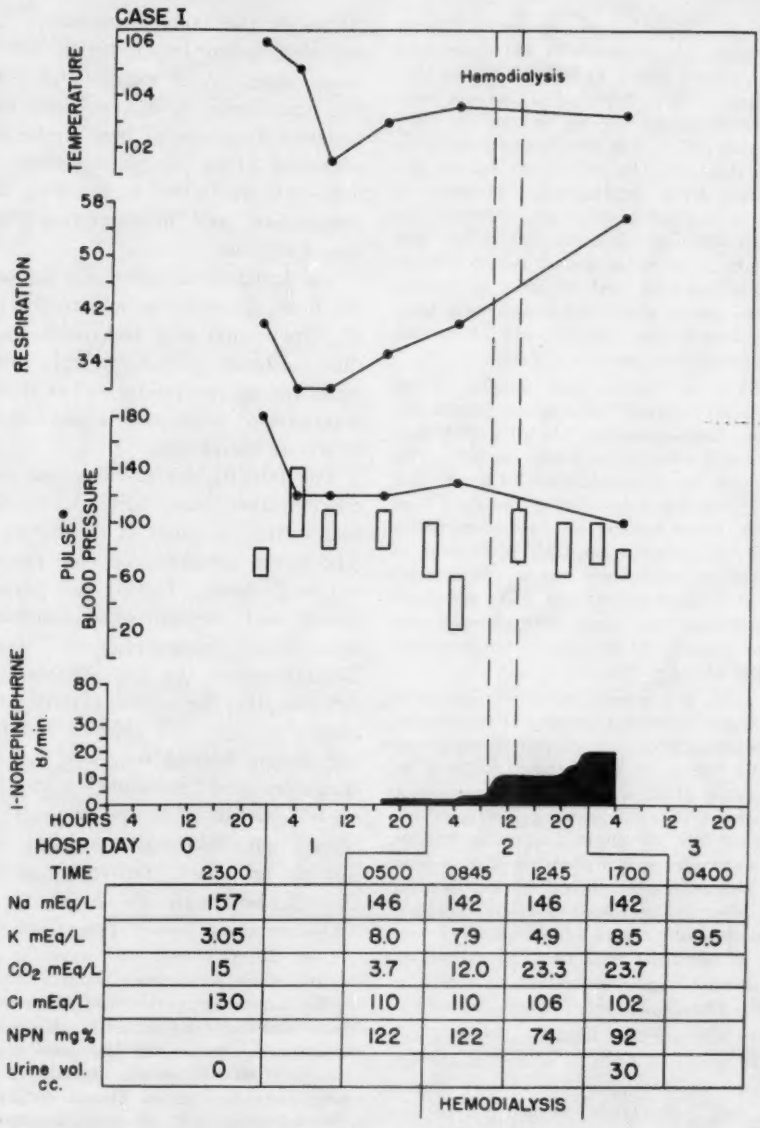


Figure 1

Two thousand cubic centimeters of 5% dextrose in water was administered intravenously during the next eight hours. During this time, the blood pressure stabilized at around 110/80 mm. of Hg; the pulse, 120 per minute, and the respiratory rate, at 30 per minute. Peripheral pulses were strong, and capillary filling was much improved. By 5 p. m., the patient was stuporous; the blood pressure was 110/100 mm. of Hg; the extremities were cold and dry; capillary filling was again poor, and cyanosis was evident. The blood pressure then fell rapidly to 80/60 mm. of Hg but was elevated to and maintained at 110/80 mm. of Hg by 2.5μg. of levarterenol per minute (1 ampule in 500 cc. of dextran at 8 drops per minute). Two thousand cubic centimeters of 5% dextrose in water was administered in the opposite arm between 5 and 12 p. m.

By 4 a. m. on the second hospital day, the blood pressure had dropped to 60/20 mm. of Hg, with a

pulse rate of 130 per minute, despite an increase in the rate of administration of the levarterenol to 10 drops per minute. At 5:50 a. m., the electrocardiogram revealed peaked T waves, intermittent atrial arrest, and an increase in QRS interval from 0.05 to 0.10 second. Blood chemistry tests were done (Fig. 1), and 3.0 gm. calcium gluconate was given intravenously, resulting in transient electrocardiographic improvement. An intravenous infusion containing 400 cc. of 50% glucose, 100 cc. of molar sodium lactate, 3.0 gm. of calcium gluconate, and 70 units of regular insulin was started while preparations were being made for hemodialysis. Arterial pH (Beckman) was 7.40 immediately prior to dialysis.

At 8:30 a. m. a four-hour dialysis on the Brigham-Kolff artificial kidney was carried out against two baths containing 135 mEq. of sodium per liter and 2 mEq. of potassium per liter. This reduced the serum potassium from 7.0 to 4.9 mEq. per liter. Sweating began during the third hour of dialysis. Blood pressure was maintained during and after the procedure by 12μg. per minute of levarterenol (4 ampules per liter of 5% dextrose in water at 12 drops per minute). Fifty milligrams of hydrocortisone was administered intravenously during the dialysis. At the close of the procedure, the arterial pH was 7.46.

By 8 p. m., the blood pressure was declining steadily despite increasing amounts of levarterenol. The clinical shock was not affected by the administration of 500 cc. of whole blood. By 10 p. m., ECG evidence of myocardial potassium intoxication recurred. At this time, serum potassium was 8.5 mEq. per liter. A solution containing dextrose, insulin, and molar sodium bicarbonate was again infused without notable clinical or electrocardiographic effect. The blood pressure gradually became unobtainable despite administration of vasopressors in increasing amounts. The patient was responsive until respirations ceased, at 4:28 a. m. on the third hospital day.

Autopsy.—Innumerable focal hemorrhages were present on all serous surfaces, in the endocardium, and around the esophagus. The kidneys weighed 250 gm. each and exhibited swollen pale cortices. Microscopically, there was central necrosis of liver cells, lipoid degeneration of both adrenals, and focal neuronal degeneration scattered throughout the brain. The proximal tubules of the kidney exhibited severe diffuse hydropic changes, while the distal convoluted tubules were filled with heme casts. The tubular epithelium showed spotty areas of irregular focal degeneration.

Comment.—For three days, symptoms attributable to heat injury were present in this patient, followed by acute psychosis. Although the body temperature was not recorded, severe hyperpyrexia was not obvious upon initial examination. Therapy was not begun until five hours after the tentative diagnosis of heat stroke made on admission to the psychiatric service. Treatment was ineffective in lowering the body temperature and in correcting the shock (see Comment).

The fact that no urine was formed from the time of admission and in the presence of hypotension and tachycardia points to the inadequacy of volume replacement with renal circulatory failure rather than to the diagnosis of acute tubular necrosis, where anuria is uncommon.

The initially depressed serum potassium concentration was first determined five hours after the onset of circulatory failure. The serum concentration rose precipitously within 27 hours. During this period, tachypnea and hyperpyrexia continued and hypotension with cyanosis supervened. Simultaneously the CO_2-combining power fell sharply. The normal arterial pH immediately prior to hemodialysis but following bicarbonate loading suggested that a severe uncompensated metabolic acidosis previously existed. The postdialysis rise of serum potassium was associated with persistence of shock, tachypnea, and hyperthermia but with no discernible fall in CO_2-combining power (see Comment).

CASE 2.—A 17-year-old recruit, a previously healthy white youth from South Texas, reported to the dispensary on the third day after entering the service early in July, 1956. He complained of weakness, headache, and abdominal cramps. He was given 1000 cc. of 5% dextrose in saline and salt tablets to take ad libitum during the day. The following day the symptoms returned and the patient was again given 1000 cc. of 5% dextrose in saline and salt tablets ad libitum. He returned to the dispensary 48 hours later, complaining of continued weakness, increasing abdominal cramps, lethargy, headache, and dizziness on arising.

Physical examinations had been negative until this visit to the dispensary, when a rectal temperature of 101 F was found. While under observation, the patient became comatose, with an unobtainable blood pressure; pulse, 180 per minute, and rectal temperature, 104 F. Immediate therapy

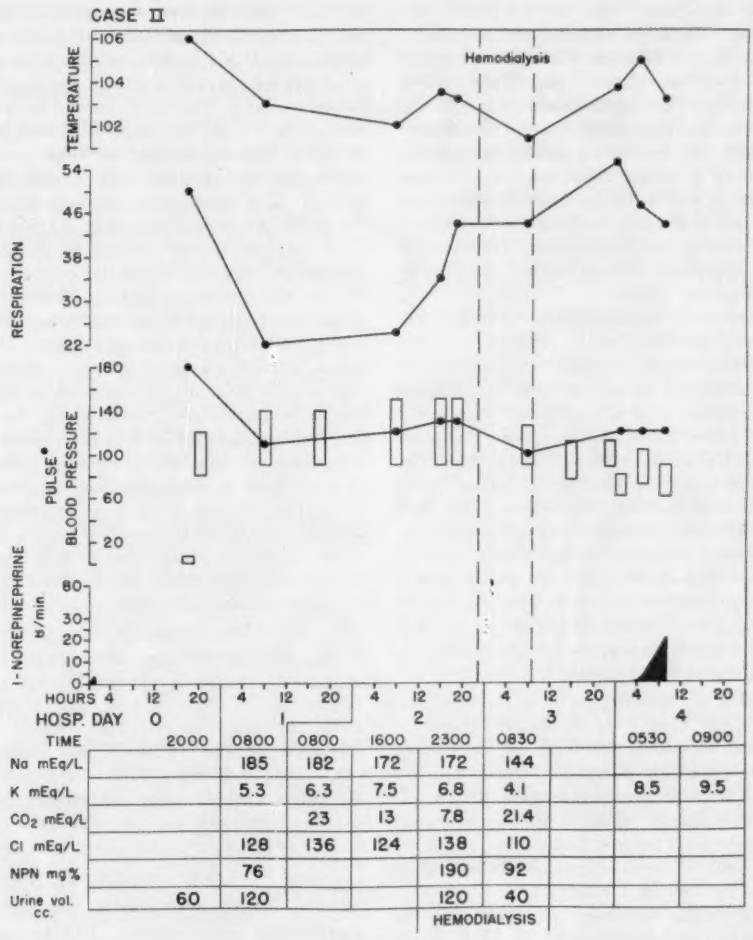


Figure 2

of 500 cc. of type O Rh-negative blood, 1000 cc. of isotonic saline, followed by levarterenol in 5% dextrose in water and 100 mg. of hydrocortisone, resulted in a blood pressure rise to 120/80 mm. of Hg and a slowing of the pulse to 120 per minute within 30 minutes. The rectal temperature remained at 104 F, and the patient was admitted to the ward.

On the morning following admission, the blood pressure was 140/90 mm. of Hg; rectal temperature, 103 F; pulse, 120 and regular. The patient was oriented but somewhat drowsy. The remainder of the physical examination was negative. The blood leukocyte count was 14,000 cubic millimeter, with 90% neutrophils and 10% lymphocytes. Urinary output was 70 cc. for the preceding 18 hours. The results of blood chemistry studies are recorded in Figure 2.

On the day following admission, the patient received 1000 cc. of isotonic saline and small quantities of water by mouth. On the second day the patient became disoriented and combative. The blood pressure rose to 150/90 mm. of Hg and the pulse, to 140 per minute but the rectal temperature remained at 103 F. One liter of 5% dextrose in water was given intravenously.

Upon return of the blood chemistry report (Fig. 2), the patient was transferred at 6 p. m. of the second hospital day to the Surgical Research Unit at Brooke Army Hospital for a possible hemodialysis. On arrival, the rectal temperature was 103 F; pulse, 150 per minute, blood pressure, 150/90 mm. of Hg; respiratory rate, 44 per minute. Physical examination revealed large areas of petechiae over the dorsum of both feet and ecchymoses at needle-puncture sites on the volar

surfaces of both arms. The mucous membranes were dull red. The orbits were full and prominent; the skin turgor was adequate. Capillary filling was slow. The chest was negative except for shallow rapid respiratory movement, with a prolonged expiratory phase and expiratory grunt. The abdomen was scaphoid and moderately tender throughout, with voluntary guarding. Neurologic examination revealed the patient to be disoriented; speech was indistinct, and swallowing, impossible; the extremities were flaccid, and deep tendon reflexes were markedly hypoactive. Fundoscopic examination was within normal limits.

Laboratory work on admission to Surgical Research Unit, Brooke Army Hospital revealed WBC, 22,000 per cubic millimeter (no differential count); hemoglobin, 15 gm. per 100 cc.; hematocrit, 44%; platelet estimation, "platelets on smear inadequate"; Lee-White clotting time, 5 minutes 30 seconds. Urinalysis, volume, 120 cc. (total volume 18 hours preceding admission); specific gravity, 1.015; acid reaction, 4+ albuminuria, with numerous RBC and granular casts in the sediment. The results of blood chemistry studies done at 6 p. m. are recorded in Figure 2. Blood glucose was 254 mg. per 100 cc. (with 10% dextrose in water running). On admission, 1000 cc. of 10% dextrose in water was given without change in the mental status or vital signs.

At 11:30 a. m., hemodialysis with the Brigham-Kolff artificial kidney was initiated against a dialysis fluid containing 140 mEq. of sodium and 4 mEq. of potassium per liter. During the first two hours, no objective improvement was noted. Physical examination remained unchanged except that the right pupil became dilated after one hour. A second bath of the same composition was begun at 1:30 a. m. During the third hour of dialysis, the patient began to sweat profusely and the blood pressure dropped slowly to 124/86 mm. of Hg; pulse slowed from 150 to 120 per minute, and verbal responses to questions were elicited. Dialysis was carried out against a third bath of the same composition, except for the reduction of potassium to 2 mEq. per liter. After five and one-half hours of dialysis, the serum sodium was 156 mEq. per liter and potassium, 5.7 mEq. per liter. A fourth bath, containing no potassium, was then begun. During the seventh hour of dialysis, the patient developed slight papilledema, and retinal hemorrhage appeared about both optic disks. At the close of dialysis, the serum sodium was 144 mEq. per liter, potassium, 4.1 mEq. per liter. During dialysis, the temperature gradually declined to 101 F. The patient, during dialysis, gained 5 lb.

During the next eight hours retinal hemorrhage increased but the neck remained supple and petechiae did not increase on the skin or appear in the mucous membranes. The blood culture done at this time was negative. A progressive decline in the systolic blood pressure occurred, reaching 112/86 mm. of Hg by 12 p. m. The pulse remained at 120 per minute; the heart size remained normal; the lungs, clear. The ECG showed no significant change. At 1 a. m., the temperature rose to 103 F; the blood pressure dropped to 90/60 mm. of Hg, and levarterenol therapy was started (2μg. per minute). The temperature remained elevated until 4 a. m., despite alcohol sponging. At that time, the blood pressure became difficult to maintain with levarterenol and the rectal temperature rose to 104 F. ECG revealed peaking of the T waves, spreading of the QRS interval from 0.04 to 0.08 second, and disappearance of P waves. An intravenous solution containing 80 cc. of molar lactate solution and 50 cc. of 50% glucose in water with 5 units of regular insulin was given. By 7 a. m., the electrocardiographic findings of potassium intoxication had diminished. However, blood pressure could not be maintained without levarterenol. At 9:21 a. m., the blood pressure became unobtainable and the heart ceased to beat, followed in a few minutes by cessation of respirations. Serum potassium in blood drawn in the closing minutes of life was 9.5 mEq. per liter.

Autopsy.—The serosal surfaces were dry and sticky. Multiple petechiae were present in almost all organs. The lungs weighed 550 gm. each, and microscopically there was a high-protein edema within the alveoli of both lower lobes. The kidneys weighed 210 gm. each and exhibited pale yellowish-tan cortices and dark brownish medulla. Microscopically the proximal tubular cells were grossly degenerated and contained pyknotic nuclei. Many tubular lumens were filled with heme casts.

Comment.—The presenting symptomatology of severe heat injury was again predominantly behavioristic. For several days, it was preceded by classical symptoms of heat exhaustion and heat cramps. However, the temperature did not reach "diagnostic levels" for heat stroke (106 F) until peripheral vascular collapse occurred. The usually acceptable treatment for heat cramps did not relieve the patient's symptoms and produced an almost pure salt excess. The patient had lost only 1 lb. during the first five days of illness, while the serum sodium concentration rose to an extreme level. The cause of initial shock was not suspected on admission; therefore, no measures were directed at the hyperpyrexia. In fact, administration of blood may have increased peripheral sludging,

thus contributing to the vascular collapse that occurred later. The levarterenol administered during the initial therapy doubtless produced peripheral vasoconstriction that, in turn, interfered with heat loss and produced a further rise in temperature. Although the treatment of shock did indeed reconstitute the plasma volume through the administration primarily of isotonic fluid, the severe deficit in total body water was not appreciated.[23]

The diagnosis of acute tubular necrosis, in this instance, seems tenable in view of persistent oliguria despite rapid resuscitation and a compatible urinalysis. Chemically the significant findings were persistent hypernatremia, a precipitous rise in the serum potassium level, and a rapidly falling CO_2-combining power. Hemodialysis against a bath containing 140 mEq. of sodium per liter lowered the serum sodium from 172 to 144 mEq. per liter, with a calculated net loss from the patient of 760 mEq. of sodium per liter and a gain of 2.5 liters of body water. The developing papilledema during dialysis suggests that rates of intracellular accumulation of water, especially in cerebral tissue, may have exceeded loss of extracellular sodium into the dialysate. A concurrent intracellular sodium shift with exchange of potassium during dialysis against a low potassium dialysate may also have occurred. Persistent hypotension and increasing hyperthermia accompanied the astonishing rise in serum potassium concentration following dialysis.

Case 3.—A 20-year-old white male recruit from New York State reported for training in August, 1956. The patient was asymptomatic until the early morning hours of the third day after his arrival. He reported to sick call complaining of headache, nausea with generalized abdominal cramps, sore throat, and backache. Physical examination revealed an oral temperature of 102 F and pharyngeal hyperemia. The patient was given 1000 cc. of 5% dextrose in saline, 600,000 units of penicillin, and symptomatic treatment. On his return to the dispensary five hours later in a confused and disoriented state, he was given 50 mg. of promazine (Sparine) intravenously and admitted immediately to the psychiatric ward at 8 p. m. On admission, his blood pressure was 130/70 mm. of Hg; rectal temperature, 102.6 F; pulse, 96 per minute; respirations, 20 per minute. Within 20 minutes his blood pressure was unobtainable; axillary temperature was 106 F; pulse, 140 per minute; respirations, 48 per minute. At this time, sponging with ice water was initiated in a fan draft, and 1500 cc. of 5% dextrose in water was given by rapid intravenous infusion. After completion of the intravenous infusions, blood pressure was maintained at approximately 100 mm. of Hg. by 80μg. of levarterenol per minute (10 ampules per liter at 30 drops per minute). The axillary temperature remained around 104 F. Laboratory data: WBC, 21,400 per cubic millimeter; differential count; 78% polymorphonuclear leukocytes, 9% lymphocytes, 5% monocytes; hemoglobin, 16.9 mm. per 100 cc. Urinalysis on 1 cc. of dark-brown urine revealed an acid pH, and a sediment loaded with RBC's and including 1 to 2 granular casts per high-power field; blood chemistry results were tabulated in Figure 3.

At 10 a. m., the axillary temperature was still 103.6 F; pulse was 110 per minute, and the respiratory rate had increased to 80 per minute. Bilateral basilar rales were noted, and 0.8 mg. of lanatoside C (Cedilanid) was given intravenously, and 1000 cc. of plasma was given, while 21μg. per minute of levarterenol (6 ampules per liter at 5 drops per minute) was required to maintain systolic blood pressure at 100 mm. of Hg. Potassium cation-exchange resin (50 gm. every six hours in 100 cc. of 10% dextrose in water) was given rectally in anticipation of rapid potassium intoxication. This regimen was continued on schedule until death.

Lumbar puncture revealed an opening pressure of 120 mm. of H_2O, no cells, sugar of 250 mg. per 100 cc., and total protein of 34 mg. per 100 cc. Temperature remained at 103 F, pulse at 140 per minute, and respirations at 52 per minute. An apical systolic murmur appeared, and despite the continued administration of oxygen by nasal catheter, the patient remained cyanotic. Through the night, the blood pressure was maintained at 110/90 mm. of Hg with 5μg. of levarterenol per minute (5 ampules per liter of 10% dextrose in water at 4 drops per minute).

At 8 a. m. of the second hospital day, 40 mEq. of molar sodium lactate was given intravenously and 40 mEq. was given orally. An additional 40 mEq. of molar lactate was given at 1 p. m. By 4 p. m., levarterenol infusion no longer provided adequate control of blood pressure, and peripheral cyanosis increased. Oxygen therapy was initiated by intermittent positive pressure. The nail beds became pink, and the patient was able to maintain a pressure of 100/50 mm. of Hg without vasopressors for approximately one hour. The blood

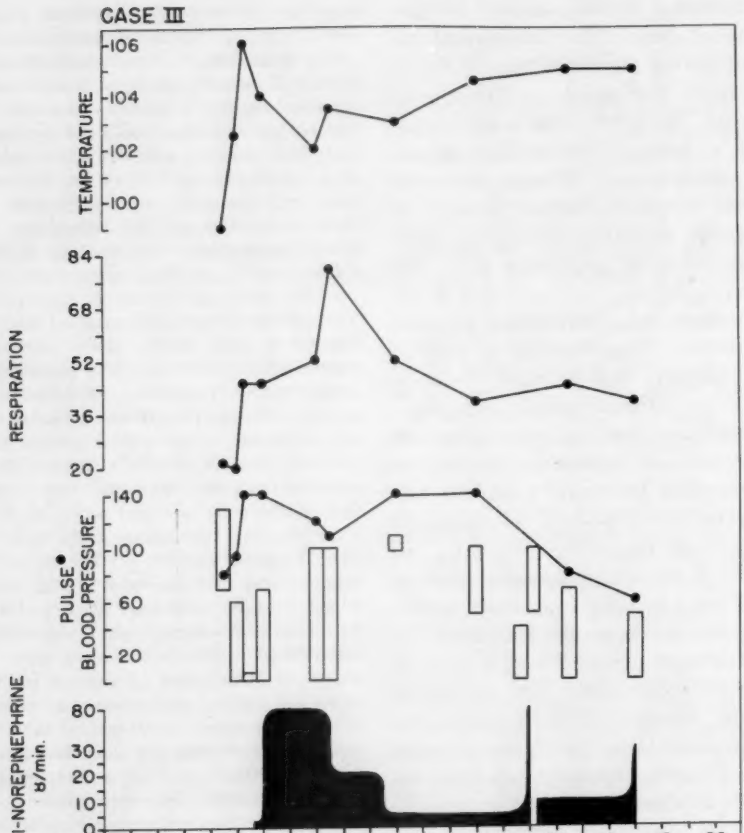


Figure 3

pressure then began to fall, and levarterenol again became necessary (10μg. to 20μg. per minute administered as 12 to 15 ampules per liter of 5% dextrose in water).

At 8 a. m. of the third day, the ECG revealed peaked T waves and a widened QRS complex (0.16 second), with atrioventricular dissociation, suggesting myocardial potassium intoxication. A serum potassium value was 6.9 mEq. per liter; consequently, 3.0 gm. of calcium gluconate was administered intravenously. The cardiac rhythm became regular. At 8:30 a. m., similar ECG findings appeared, and 1.0 gm. of calcium gluconate was administered rapidly, resulting in the conversion of the rhythm to normal for approximately five minutes. The atrioventricular dissociation returned, with multiple premature ventricular contractions. No response was obtained from giving additional calcium gluconate. Suddenly the ECG revealed typical ventricular fibrillation.

Autopsy.—Serosal surfaces and the mucosal surfaces of most organs were covered by petechial hemorrhages. Central lobular necrosis of hepatic cells was present. The lungs weighed 500 gm. each, and basilar alveoli were filled with edema of a high-protein nature. The kidneys weighed 230 gm. each; the cortices were pale and swollen. Microscopically the distal tubular lumen was filled with heme casts. The distal tubular epithelium was degenerate and contained pyknotic nuclei. Focal neuronal degeneration was scattered throughout the nervous tissue.

Comment.—Although symptoms were apparently present for only 12 hours prior to admission, it is likely that prodomal manifestations of heat injury were present for a longer period. Again the presenting symptoms were behavioristic, and severe hyperpyrexia occurred only with circulatory failure. It is noteworthy that the initial error in diagnosis resulted in inappropriate fluid therapy. Although the diagnosis of heat stroke was suspected later, neither hyperthermia nor shock had been controlled. Inadequate volume replacement and use of levarterenol impaired adequate dissipation of heat. The severe volume deficiency is indicated by the hemoconcentration, hypernatremia, and hyperchloremia. These initial chemical determinations were done after the administration of 2 liters of 5% dextrose in water.

Persistent oliguria is again attributable to shock, as in Case 1. The diagnosis of acute tubular necrosis is untenable without adequate resuscitation from shock.

Although the clinical deterioration was continuous, chemical changes on the second hospital day were particularly dramatic. Serum potassium rose rapidly in spite of the use of large quantities of potassium-exchange resins. (Cation-exchange resins have proved effective in preventing rapid accumulation of potassium in patients with acute renal failure.) Although the final serum potassium obtained was only slightly elevated, the cardiotoxic findings noted in the ECG were compatible with severe hyperkalemia, suggesting that either there was a laboratory error or other factors affected the cardiac conduction mechanism in a similar manner.

Comment

Persistence of Symptoms Attributable to Heat Injury.—This persistence, following initial diagnosis on sick call, indicates that treatment by intravenous or oral salt solutions alone may be inadequate to prevent further disability imposed by a heat load.[6,7,11] When remission of symptoms and signs does not occur within 24 hours, hospitalization is necessary. This will permit removal of heat stress imposed by a hot environment; observation of the patient's mental status, his vital signs, and urinary output, and replacement of fluid volume and electrolytes guided by the clinical findings and blood chemical determinations. Otherwise minor heat injury may progress to heat stroke manifested by either classical or atypical clinical features.

Two vital principles in treatment of heat stroke are the rapid reconstitution of circulating blood volume and rapid lowering of temperature. The potential volume of the vascular tree in heat stroke is greatly increased by cutaneous and muscular vasodilatation.[2] Rapid administration of large quantities of salt and water are, therefore, required to meet the discrepancy between the existing blood volume and the expanded vascular space. The quantities necessary to meet this need may be greatly reduced, however, by rapidly dissipating body heat. This is best accomplished in severe cases by immersion in ice water until temperature falls below 101 F.[14] Alcohol sponging may be effective when shock and excessive hyperpyrexia are not present. This can be accomplished when several persons rub vigorously with iced alcohol sponges in an adequate draft. These two measures—reconstitution of vascular volume and rapid lowering of the body temperature—will result in resuscitation from the shock of severe heat injury. In contrast, it is obvious that administration of levarterenol in the initial phases of therapy is contraindicated

on the grounds that the generalized increase in peripheral vasoconstriction reduces the blood flow to the skin,[19] thereby impairing heat loss and accentuating the basic physiologic defect. From this clinical setting of persistent shock and hyperpyrexia in Cases 1 and 3, and even with transitory recovery from the shock in Case 2, a progressive downhill course occurred that was characterized clinically by coma, tachycardia, tachypnea, oliguria, and chemically by fulminating hyperkalemia and metabolic acidosis.

Hypernatremia.—Hypernatremia preceding or accompanying heat stroke may influence the clinical picture. Twelve of the one hundred cases reported by Austin and Berry[1] had an elevated serum sodium. In those, as in the three cases reported here, the central nervous system symptoms were extremely severe. Temperature elevations were uniformly lower than the diagnostic heat stroke level of 106 F. Uremia, hypotension, and, in four cases, hyperkalemia also existed.

Extreme elevations of serum sodium concentration in these cases arose from prolonged excessive loss of hypotonic sweat water, sodium chloride administration, and probably a net positive sodium balance resulting from oliguria accompanying serum hypertonicity.[23]

The extracellular fluid volume is maintained by virtue of its hypertonicity for a relatively long period at the expense of a constantly increasing intracellular water loss of severe proportions.[3] Maintenance of the extracellular fluid space results in a paucity of clinical findings, thus delaying recognition and treatment. Thus, the clinical course suggests that the presenting central nervous system symptoms[15] may have resulted from hypernatremia.

Acute Renal Failure.—Other reports of patients with heat injury[1,10,16,17,22] cite a small but definite incidence of oliguria and a histologic picture of acute tubular necrosis. Its development has not been correlated with the observed clinical course. The histologic changes of acute tubular necrosis were present in all three of these cases. However, in contrast to Case 2, an antemortem diagnosis could not be made in Cases 1 and 3 in the presence of shock. In Case 1, the presence of anuria and hence the inability to demonstrate renal tubular casts in the urinary sediment made this diagnosis untenable. Renal ischemia over a prolonged period accompanied by a persistent shock, however, may account for histologic tubular necrosis.

Cause of Death.—Although comparable cases of heat injury have been reported,[1,17] often the actual cause of death has not been determined. In Cases 1 and 2, and probably in Case 3, death was directly attributable to persistent circulatory failure and myocardial potassium intoxication. Few data have been published on serum potassium levels in patients sustaining heat injury. Reported determinations are not stated in the time relationship to the clinical picture. Early in the course, reported values are generally low (less than 4 mEq. per liter). Austin and Berry[1] reported 4 of 44 potassium determinations in excess of 5 mEq. per liter and stated that all of these patients died. Balance studies in asymptomatic unacclimatized men during periods of heat stress revealed that potassium is excreted in excess of nitrogen derived from tissue break-down.[2,8] Urinary excretion of potassium increased threefold, while the potassium concentration of sweat was extremely high, often accounting for 50% of the total potassium intake.[5] Hence the exposure to heat may accelerate movement of potassium out of cells, and the serum concentration will depend largely on the integrity of the potassium excretory mechanisms of sweat glands and kidney. Also it is conceivable that the high serum potassium concentrations observed in these patients might be related to the presence of metabolic acidosis which supervened rapidly in these patients,[4] since sodium will exchange for intracellular potassium in this setting. Note, however, that the post dialy-

sis potassium elevation in Case 1 occurred without a concurrent fall in plasma CO_2-combining power. Daily rises in serum potassium concentration of this magnitude have not been reported previously in patients with acute renal failure alone,[20] nor have they been recorded in cases of heat injury. In patients with post-traumatic renal insufficiency in whom rapidly developing potassium intoxication was common, the average daily potassium rise was 0.7 mEq. per liter per day, with a range of 0.0 to 3.0 mEq. per liter per day.[21] Abrupt elevations of 1 to 1.5 mEq. per liter in 24 hours have been observed in terminal uremia. In animals, traumatic shock resulted in potassium rises of 1.5 mEq. per liter in eight hours, with a terminal rise of 3.1 mEq. per liter during the last one and one-half hours.[12,24] Therefore, in the patients presented here, hyperkalemia may have resulted from a combination of factors: (1) cellular destruction resulting from prolonged hyperthermia and severe tissue hypoxia secondary to shock (a rapid rise in NPN occurred); (2) hypernatremia with subsequent extracellular movement of potassium; (3) destruction of sequestered heat-damaged red blood cells, and, finally, (4) the extracellular movement of potassium in response to severe decompensated metabolic acidosis.

Summary and Conclusions

Patients having apparently minor symptoms who do not respond promptly to usual therapy are candidates for severe heat stroke.

Atypical heat stroke may occasionally present itself clinically as an acute mental disorder without severe hyperpyrexia. It is suggested that the accompanying severe hypernatremia may be partially responsible for these symptoms.

Two vitally important objectives in the therapy of heat stroke are rapid lowering of the body temperature and immediate reconstitution of plasma volume. Whole blood and levarterenol are contraindicated for the reasons discussed.

The diagnosis of acute tubular necrosis should not be made unless oliguria persists after complete resuscitation from shock.

Without a prompt diagnosis and vigorous therapy, a bizarre clinical picture may result, including shock, oliguria, and continued hyperpyrexia, with abrupt elevations in serum potassium concentration.

Death in these cases probably resulted from fulminating myocardial potassium intoxication.

U. S. Army Surgical Research Unit, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

REFERENCES

1. Austin, M. G., and Berry, J. W.: Observations on 100 Cases of Heatstroke, J. A. M. A. 161:1525, 1956.

2. Bass, D. E.: Mechanisms of Acclimatization to Heat in Man, Medicine 34:23, 1955.

3. Black, D. A. K.; McCance, R. A., and Young, W. F.: A Study of Dehydration by Means of Balance Experiments, J. Physiol. 102:406, 1944.

4. Brunell, J. M.; Villamil, M. F.; Uyena, B. T., and Scribner, B. H.: The Effect in Humans of Extracellular pH Change on the Relationship Between Serum Potassium Concentration and Extracellular Potassium, J. Clin. Invest. 35:935, 1956.

5. Conn, J. W.; Johnston, M. W., and Louis, L. H.: Acclimatization to Humid Heat: A Function of Adrenal Cortical Activity, J. Clin. Invest. 25:912, 1956.

6. Conn, J. W.; Johnston, M. W., and Louis, L. H.: Relationship Between Salt Intake and Sweat Salt Concentration Under Conditions of Hard Work in Humid Heat, Fed. Proc. 5:230, 1946.

7. Eichna, L. W.; Park, C. R.; Nelson, N.; Horvath, S. M., and Palmes, E. D.: Thermal Regulation During Acclimatization in a Hot Dry (Desert Type) Environment, Am. J. Physiol. 163: 585, 1950.

8. Elkinton, J. R., and Winkler, A. W.: Transfers of Intracellular Potassium in Experimental Dehydration, J. Clin. Invest. 23:93, 1944.

9. Ferris, E. O., Jr.; Blankenhour, M. A.; Robinson, H. W., and Ceelles, G. E.: Heat Stroke—Clinical and Chemical Observations on 44 Cases, J. Clin. Invest. 17:249-261, 1938.

10. Gauss, H., and Meyer, K. A.: Heat Stroke: Report of 158 Cases from Cook County Hospital, Chicago, Illinois, Am. J. M. Sc. 154:554-564, 1917.

11. Harrison, T. R., and Daily, W. M.: Experimental Hyperpyrexia, Am. J. M. Sc. 154:554-564, 1938.

12. Holmes, J. H.: The Relation of Serum Potassium to Shock in Dogs Subjected to Muscle Trauma, Am. J. Physiol. 148:449, 1947.

13. Kanter, G. S.: Effect of Heat on Regulation of Body Fluid and Electrolytes in Dogs, Am. J. Physiol. 178:259, 1954.

14. Ladell, W. D., and Waterlow, J. C.: Desert Climate: Physiological and Clinical Observation, Lancet 2:491 and 529, 1944.

15. Luetscher, J. A., and Blackman, S. S., Jr.: Severe Injury to the Kidneys and Brain Following Sulfathiozole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. 18:741, 1943.

16. Malamud, N.; Haymaker, W., and Custer, R. P.: Heat Stroke: Clinopathologic Study of 125 Fatal Cases, Mil. Surgeon 99:397, 1946.

17. Marchand, W. E., and Riemer, O. L.: Intravenous Procaine Hydrochloride in the Therapy of Acute Renal Insufficiency Following Heat Stroke: Case Report, Mil. Surgeon 105:475, 1949.

18. Mendeloff, A. I., and Smith, D. E.: Extreme Physical Effort in Summer Heat Followed by Collapse, Stupor, Purpura, Jaundice and Azotemia, Am. J. Med. 18:659, 1955.

19. Moyer, J. H.; Skelton, J. M., and Mills, L. C.: Nor-Epinephrine: Effect on Normal Subjects; Use in the Treatment of Shock Unresponsive to Other Measures, Am. J. Med. 15:330, 1953.

20. Strauss, M. B.: Acute Renal Insufficiency Due to Lower-Nephron Nephrosis, New England J. Med. 239:693, 1948.

21. Teschan, P. E.; Post, R. S.; Smith, L. H., Jr.; Abernathy, R. S.; Davis, J. H.; Gray, D. M.; Howard, J. M.; Johnson, K. E.; Klopp, E.; Mundy, R. L.; O'Meara, M. P., and Rush, B. F., Jr.: Post-Traumatic Renal Insufficiency in Military Casualties: I. Clinical Characteristics, Am. J. Med. 18:172, 1955.

22. Wilcocks, C.: Heat Stroke and Allied Conditions, Practitioner 147:463, 1941.

23. Winkler, A. W.; Ellington, J. R.; Hopper, J., Jr., and Hoff, H. E.: Experimental Hypertonicity: Alterations in the Distribution of Body Water and the Cause of Death, J. Clin. Invest. 23:103, 1944.

24. Winkler, A. W., and Hoff, H. E.: Potassium and the Cause of Death in Traumatic Shock, Am. J. Physiol. 139:686, 1943.

25. Adolph, E. F., et al.: Physiology of Man in the Desert, New York, Interscience Publishers, Inc., 1947.

A Review of the Current Status of Nonoperative Cholecystoangiography

EDWIN M. COHN, M.D., and DAVID M. SKLAROFF, M.D., Philadelphia

Several years ago, a striking advance in radiologic examination of the biliary tract enabled the common duct to be visualized by a new solution administered intravenously.[1] Shortly thereafter it was learned that the biliary tract could be outlined in the absence of the gallbladder.[2] This new technical accomplishment was made possible by a rather highly concentrated iodine derivative, prepared as a solution and administered intravenously. Iodipamide (Cholografin) methylglucamine is a colorless solution of the bis N-methylglucamine salt of 3-3′-(adipoyldiimino) bis (2,4,6-triiodobenzoic acid). Since its introduction, different techniques have been employed in order to obtain the best radiographic reproduction of the biliary tract, criteria have been established in order to standardize interpretations, and, with the ever-increasing number of examinations, information has been accumulated to evaluate the advantages and limitations of this diagnostic procedure.

Iodipamide, being isotonic, is administered intravenously and under normal conditions is excreted promptly by the liver. As early as 10 minutes after completion of the injection, concentration of this radiopaque medium may be sufficiently intense to permit identification of the common duct. Moving with the bile, it passes into the intestinal tract and is excreted in the stool, without traveling through the enterohepatic circulation. In about 10% of examinations, a nephrogram will appear,[3] and this percentage will increase when iodipamide is used in the presence of liver disease.

Submitted for publication Oct. 11, 1957.

Associate in Gastroenterology (Dr. Cohn) and Associate in Radiology (Dr. Sklaroff), Albert Einstein Medical Center, Northern Division.

Technique

The most widely used and generally accepted technique begins by preparing the patient with a laxative, such as compound senna (licorice) powder, the night prior to the examination, followed by a saline enema the next morning. Food and liquids are withheld for a period of 12 hours preceding the examination. As a precaution against allergic reactions a test dose of 1 cc. of iodipamide is given intravenously. If no evidence of sensitivity appears within 15 minutes, a total dose of 20 cc. is injected very slowly, over a period of 10 minutes. The first film is obtained 10 minutes after the completion of the injection. It is developed immediately and viewed while wet. Thereafter, additional exposures are made at intervals of 10 minutes up to 40 minutes, at which time the study of the common duct should be completed. During the examination, rotation of the patient may be required in the erect, recumbent, and lateral decubitus positions to separate interfering shadows of overlying ribs and intestinal gas from portions of the common and hepatic ducts. Often the degree of opacification may be increased by the hypodermic injection of morphine sulfate (1/6 grain [11 mg.]) which apparently exerts a spastic effect on the terminal segment of the common duct. Visualization will frequently be enhanced by the utilization of the planigraphic technique.[4] Where a gallbladder is intact, a cholecystogram, also, may be obtained by roentgenograms one-half to two hours after the iodipamide has been injected.

Several modifications of this procedure have been suggested. One author believes that by combining iopanoic acid (Telepaque) and iodipamide less time would be required to demonstrate the gallbladder and the ductal system.[5] The patient is instructed to swallow iopanoic acid tablets after a fat-free evening meal. The films are taken the next morning, whereupon 20 cc. of iodipamide is injected intravenously. After 30 minutes another x-ray film is obtained; a fatty meal is ingested, and a final film is taken 30 minutes later. If the gallbladder is not visualized, an additional 20 cc. of iodipamide is administered. By such a technique, the results were considered to be satisfactory in 95 of 100 unselected cases. Thirty minutes after the initial injection of iodipamide 67 cases were

adequately visualized, and after a fatty meal 32 additional cases became opacified.

Another suggested method employs two separate injections of iodipamide at two and one-half- to three-hour intervals in order to demonstrate the gallbladder and biliary duct with the same approximate degree of intensity.[6] The film is taken only after the second injection.

Reactions

If iodipamide inadvertently is injected into the tissue around the vein, a painful inflammatory reaction is promptly created, but this responds readily to the application of hot compresses. There has been no evidence of thrombophlebitis of the vessel through which the substance was injected. Systemic reactions have consisted of nausea and occasionally vomiting. Invariably, the injection given too rapidly was believed to have been responsible for a reaction. In cases of extreme sensitivity to iodipamide, peripheral circulatory effects of varying degrees of severity have occurred, but this type of reaction has been controlled successfully by the use of sedation, antihistamine, or epinephrine. A satisfactory precautionary measure is to inject intravenously 1 cc. of the dye to determine the sensitivity of the patient. If no reaction occurs, the entire dose of iodipamide may be administered.

Applications

In considering the uses and advantages of iodipamide, the one outstanding contribution is the ability to investigate the biliary tract after cholecystectomy to determine whether symptoms which persist are associated with disease of the ductal system.[7] This type of examination not only is feasible but can be accomplished without additional operative intervention intended solely for diagnostic purposes. Much of the confusion regarding the postcholecystectomy syndrome, therefore, has been clarified to a large extent by certain positive findings in the biliary tract. Some of the abnormalities which have been detected include common-duct dilatation, residual calculi, postoperative ductal deformities, and gallbladder remnants or re-formed gallbladder.

The several handicaps imposed by the ingestion of tablets which occasionally interfere with successful carrying out of the roentgen examination of the biliary tree may be avoided by the use of iodipamide. The intravenous administration of iodipamide eliminates the variable factor of intestinal absorption, circumvents the interference imposed by pyloric obstruction, and overcomes the difficulty encountered in some persons who cannot swallow tablets. In addition, since iodipamide is used in a physiologic manner, it demonstrates the patency of the sphincter of Oddi by its presence in the small intestine. It has been used my some authors to investigate the functioning capacity of an end-to-end anastomosis of the common duct performed for stricture.

There has been no consistent relationship between visualization of the gallbladder and of the common duct after iodipamide. Failure to obtain opacification of an intact gallbladder does not preclude a successful radiologic study of the common duct. Just as the common duct has been demonstrated in the absence of a gallbladder, so too may the biliary tract be demonstrated when a gallbladder is present but diseased, which in a very high percentage of cases is so diagnosed by the very fact that it cannot be visualized. Inability to outline the common duct by radiographic techniques need not, therefore, be due to an abnormal gallbladder but may be found in hepatic disease, marked hyperbilirubinemia,[3] or other factors which, at present, are not entirely explained.

The diagnosis of biliary dyskinesia is usually made with difficulty and has been questioned by many. Doubilet and Mulholland[9] have reported cases in which pain due to obstruction of the distal end of the common duct was related to spasm. During the course of a previous study,[10] functional changes were demonstrated in patients to whom morphine was given in an effort

to increase the degree of opacification of the common duct. While this was accomplished, the duct by actual measurement distended to almost twice its original size. At the same moment, one patient complained of sudden excruciating pain referred from the right upper quadrant of the abdomen straight through to the back. This was the same pain of which she had complained for many years and which had remained unexplained. In another patient, when the same effect was produced, glyceryl trinitrate was given sublingually. Not only was the pain relieved, but films obtained at the same time demonstrated the return of the common duct to its original width as the contrast medium poured into the duodenum. The simultaneous recording of symptoms and demonstration by means of iodipamide of the spasticity of the sphincter of Oddi together with common duct distention has strengthened the acceptance of biliary dyskinesia as a clinical entity.

Fistulas have been reported as being recognizable after the administration of iodipamide by the appearance of the dye outside the confines of the normal anatomy of the biliary tract.[11]

Wherever a prompt decision must be made in the presence of an acute abdominal emergency, the speed in producing roentgenograms of the biliary ducts and gallbladder becomes of utmost importance.[12] Intravenous administration of iodipamide makes this possible. The ability to visualize the biliary tract very likely precludes disease there and eliminates one of the considerations in a differential diagnosis of abdominal symptoms.

The effectiveness of iodipamide compared to iopanoic acid for visualizing the biliary tract, including the gallbladder, has been studied.[13] In one series of cases, the gallbladder was visualized with iodipamide in 12 out of 34 patients in whom poor visualization or no visualization resulted after the oral administration of iopanoic acid. It was interesting to observe that in 22 of the 34 cases the gallbladder was not visualized with iodipamide but there was good visualization of the ducts. Twelve of these patients were operated on, and the cystic duct was found to be obstructed in ten. In another study of 68 symptomatic patients, the gallbladder was visualized in 35% of patients after the use of iopanoic acid and in 57% of cases after iodipamide. Intravenous cholecystography, therefore, proved to be of greater value in cases in which gallbladder visualization was poor or absent after oral administration of the opaque material. The latter method, however, as a routine measure retains the advantage of ease of administration and time-saving feature.

Tumors of the biliary duct system and of the head of the pancreas have been detected by intravenous cholangiography.[14] A filling defect within the lumen of the duct must be considered in terms of neoplasm if calculi can be ruled out. The intimate relation of the common duct to the pancreas has provided a rather characteristic course of the common duct as it appears on film after the administration of iodipamide. The appearance of compression from extrinsic cause and/or deviation in the usual course of the common duct has been suggested as a pathognomonic sign of enlargement of the head of the pancreas.

As another opportunity to increase the accuracy of examination of the common duct, iodipamide may be employed preoperatively to add to the diagnostic approaches for a more complete evaluation of this segment of the biliary tract, which later may be supplemented by direct visualization and operative cholangiography.

Disadvantages

There are, however, certain disadvantages which have been recognized in the use of iodipamide. The inconvenience of intravenous administration is an appreciable factor, particularly when compared with the relative ease of taking tablets by mouth. The higher basic cost of the examination remains as an item for consideration. More

time is required because of the advisability of closer supervision in carrying out the actual technical procedure.

Stratification has been noted to occur between the radiopaque medium and the nonopaque bile, particularly when films are taken while the patient is in an erect position. This phenomenon acts as a source of confusion because of its similarity to the layering effect of floating calculi. Better clarification, however, may be obtained by the use of a fatty meal. On occasions, the gallbladder has been reported to be normal even though it may contain tiny stones undetected in a denser opacification created by iodipamide. Also, the inability of the gallbladder to show varying degrees of shadow density and/or diminution in size may offer presumptive evidence of failure of the gallbladder to concentrate. Finally, the regurgitation of this radiographic medium into the duodenal bulb has simulated a gallbladder in a patient who supposedly has undergone a cholecystectomy.

Limitations

In addition to the disadvantages, certain limitations have been recognized in the use of iodipamide, some of which also hold for roentgen examination of the biliary tract by the oral method and some of which are peculiar to iodipamide itself. One of the more important limitations, for example, has been the inability to obtain satisfactory visualization of the biliary tract in the presence of jaundice. This handicap is all the more lamentable since jaundice may be explained by disease in the extrahepatic biliary tree. While it was formerly believed that any abnormal degree of icterus would preclude the opacification of the biliary tree, experience has enabled us to realize that an acceptable examination often has been achieved in the lower levels of jaundice. A serum bilirubin level above 5.0 mg. per 100 cc. invariably will be associated with failure to outline the biliary ductal system by iodipamide.[16] Moreover, significant liver damage without jaundice likewise will offer another limitation to a completely adequate x-ray study. The sulfobromophthalein (Bromsulphalein) test measuring the amount of liver disease offers no sharp line of demarcation where the likelihood of visualization can be predicted with reasonable accuracy. Although in a vast majority of instances a sulfobromophthalein retention of more than 40% will be associated with a nonvisualized biliary tract, cases have been reported where the roentgen examination was considered a failure with the sulfobromophthalein test of 6% retention and a serum bilirubin value of 1.0 mg. per 100 cc. Among the other limitations of intravenous cholangiography is the failure to visualize the retained cystic duct stumps that are obstructed by nonopaque calculi. Similarly, nonopaque calculi in the large bile ducts have escaped detection, while opaque stones less than 1 cm. in diameter may often be unrecognizable. Shortly after the introduction of iodipamide, it was realized that there was a consistent failure to visualize the terminal portion of the common duct, an area which continues to be a blind spot despite many attempts of new techniques to delineate it more clearly. Finally, there seems to be a greater opportunity for erroneous or equivocal interpretation of the x-ray findings in the biliary tree as compared to the statistics relative to cholecystography when oral routes of administration of the dye alone are employed.

Evaluation

The care and persistent accuracy of the roentgen interpretation following the administration of iodipamide will add to the confidence and reliability with which one employs this new diagnostic medium. In the numerous studies which have been undertaken to evaluate the accuracy of x-ray findings after ingestion of tablets, a fairly close approximation has been made of how many visualized gallbladders with stones will have stones at the operating table and how many nonvisualized gallbladders are

associated with calculi. In the somewhat limited study of 114 cholecystectomized patients [11] in whom an intravenous cholangiogram had been performed to confirm or exclude clinically suggested pathologic changes in the biliary tree, a positive or confirmatory diagnosis was made in 54, or 47%; was essential in making the diagnosis in 18 cases, or 15%; failed to visualize the biliary tract in 17, or 14%; was of equivocal value in 17 cases, or 14%, and proved to be erroneous in 8 cases, or 7%. If statistics were to be compiled after eliminating patients with jaundice or recognized liver damage which might be expected to interfere with adequate visualization of the biliary tree, the accuracy of useful cholangiography in demonstrating or excluding disease of the bile duct in the postcholecystectomized group of patients has been reported to be 86%. In regard to the efficacy of detecting stones, the visualized intravenous cholangiograms reported stones in 50% of cholecystectomized patients who were reexplored because of suspected residual common-duct stone which was proven at operation. An interesting study was reported of eight patients with acute cholecystitis who were examined shortly after the onset of symptoms. Not one demonstrated a visualized gallbladder, but the ductal system could be outlined in five patients.

One of the findings which has evolved since the introduction of intravenous cholangiography and has brought forth a considerable amount of speculation as to its meaning is the size of the common duct. In the cholecystectomized patient one report considers a common duct larger than 7 mm. to be dilated, while another author found the average size of the duct in the absence of disease to be 10 mm. No constant relationship could be recognized between the size of the common duct and the time elapsed since cholecystectomy. On the basis of size, therefore, obstruction of the common duct whose width is less than 8 mm. is extremely unlikely.[17] Since 82 out of 142, or 57%, of visualized common ducts studied in cholecystectomized patients were found to measure between 8 and 15 mm., the size of the common duct in this group is considered not to be significant in determining the presence or absence of obstruction. However, when the common duct is found to have a width of 15 to 30 mm., partial obstruction is likely to exist. According to one study regarding this width of common duct, stones were found in 9 out of 10 patients. In addition to the size of the common duct, other criteria have been considered for evaluating the intravenous cholangiogram. One of the criteria is the time-density factor, which depends on a comparison of the degree of ductal opacity measured every 15 minutes for 120 minutes after the administration of iodipamide. If the common duct is partially obstructed at its distal end, the density of the dye at the end of 120 minutes will not be significantly less than the density at 60 minutes. At this time it might be well to point out that the need for morphine, which was recommended previously as part of the technique to increase the degree of opacification of the common duct, be reevaluated. The administration of morphine would destroy the concept of time-density relationship by creating a pharmacological obstruction. Some attempt has been made to estimate the amount of dye in the duodenum as an index of the degree of obstruction, but this has proven to be so variable that little importance has been associated with this finding. The morphology of the ductal system has been scrutinized to suggest the possible presence of any abnormality. For example, the obstructed common duct has been found usually to be somewhat more tortuous than the unobstructed duct. Also, when the hepatic radicles are visualized, they appear to be slightly blunted. Other positive findings, of course, must be included in the list of criteria in the examination of the intravenous cholangiogram. These consist of the cystic duct stump and gallbladder remnant and stones which are visualized directly if they are radiopaque or as filling defects if nonopaque.

Summary

Intravenous cholangiography is useful in the study of patients who continue to present symptoms referable to the biliary tract after cholecystectomy.

Intravenous cholecystoangiography may be employed preoperatively to determine the presence of calculi in the common duct.

The administration of iodipamide (Cholografin) offers advantages in visualizing the gallbladder after unsuccessful results with oral cholecystographic media.

Iodipamide is preferred when patients are unable to swallow tablets, in small-bowel disease with interference in obstruction, in pyloric obstruction, and in emergencies when speed is a factor of importance.

The limitations of carrying out biliary tract studies with iodipamide include layering, the presence of jaundice, liver disease, and inability to visualize the terminal portion of the common duct.

Certain disadvantages inherent in employing iodipamide for opacification of the biliary tract are enumerated.

Criteria for evaluating information obtained by iodipamide are presented.

The significance of the size of the common duct after cholecystectomy is discussed in relation to its diagnostic import.

Tabor Medical Building, 1315 Tabor Rd. (41).

REFERENCES

1. Frommhold, W.: Ein neuartiges Kontrastmittel für die intravenöse Cholezystographie, Fortschr. Geb. Röntgenstrahlen 79:283, 1953.

2. Sklaroff, D. M.; Cohn, E. M.; Orloff, T. L., and Gershon-Cohen, J.: The Common Bile Duct in the Postcholecystectomy Patient, A. M. A. Arch. Surg. 70:559, 1955.

3. Shehadi, W. H.: Intravenous Cholecystocholangiography, J. A. M. A. 159:1350, 1955.

4. Orloff, T. L.: Intravenous Choledocholaminography, Am. J. Roentgenol. 2:804, 1954.

5. Mitchell, D. J.: Basic Combined Cholecystangiography, Brit. J. Radiol. 29:133, 1956.

6. Lajos, S.: Durch Biligrafin eröffnete neue Wege für die Röntgenuntersuchung des Gallensystems, Fortschr. Geb. Röntgenstrahlen 83:776, 1955.

7. Orloff, T. L.; Sklaroff, D. M.; Cohn, E. M., and Gershon-Cohen, J.: Intravenous Choledochography with a New Contrast Medium, "Cholografin." Radiology 62:868, 1954.

8. Jordan, P. H.: The Use of Intravenous Cholangiocholecystography in the Diagnosis of Acute Conditions of the Abdomen, Surg. Gynec. & Obst. 102:218, 1956.

9. Doubilet, H., and Mulholland, J. H.: Recurrent Acute Pancreatitis, Ann. Surg. 128:609, 1948.

10. Cohn, E. M.; Orloff, T. L.; Sklaroff, D. M., and Gershon-Cohen, J.: The Use of Cholografin in the Postcholecystectomy Syndrome, Ann. Int. Med. 42:59, 1955.

11. McDonough, F. E., and Wise, R. E.: Limitations of the Clinical Application of Intravenous Cholangiography in Determining Disease of the Bile Ducts After Cholecystectomy, Gastroenterology 29:771, 1955.

12. Sparkman, R. S., and Ellis, P. R.: Intravenous Cholecyst-Cholangiography in Emergency Abdominal Diagnosis, Ann. Surg. 143:416, 1956.

13. Kremens, V.; Berger, S. M., and Cohn, E. M.: Comparison of Rapid Intravenously and Orally Administered Contrast Mediums for Routine Gall Bladder Study, New England J. Med. 254:705, 1956.

14. Kantor, H. G.; Evans, J. A., and Glenn, F.: Cholangiography: Critical Analysis, A. M. A. Arch. Surg. 70:237, 1955.

15. Aldridge, N. H.: Cholecystography and Cholangiography: A Review of Present Methods of Examination, Am. J. M. Sc. 231:701, 1956.

16. Cohn, E. M.; Berger, S. M., and Kremens, V.: Cholecystography in the Presence of Jaundice, Ann. Int. Med. 46:53, 1957.

17. Wise, R. E., and O'Brien, R. G.: Interpretation of the Intravenous Cholangiogram, J. A. M. A. 160:819, 1956.

Tuberculosis, a Disease of Old Age

ROBERT G. BLOCH, M.D., New York

Since the beginning of this century and especially since the most recent advances in the battle against tuberculosis through effective chemotherapy, the age distribution of the disease has changed radically in those parts of the world where a concerted attack on tuberculosis has been possible. The first great change was accomplished through effective sanitation of the milk supply, which resulted in practically complete control of bovine tuberculous infection in a few countries, notably the United States; the secondary manifestations of bovine infections, particularly tuberculous osteomyelitis, have since become comparatively rare.

This achievement in combination with the enlightened concept that the exposure to the human bacillus in home life is the main source of clinical pulmonary tuberculosis resulted in a decline of the mortality among children to very low values even before the era of chemotherapy. American statistics show a remarkable decrease from about 200 deaths in children per 100,000 population between 1900 and 1954. During the past decade it has almost reached the zero point.

The decline of the mortality curve for the total population during the past 50 years which has proceeded at an even pace with elevations only during the two world wars (Chart 1) shows some of the factors which

Submitted for publication Sept. 9, 1957.

The National Tuberculosis Association provided statistical material.

From the Division of Pulmonary Diseases, Montefiore Hospital.

This publication was supported by the Jesse Michel Memorial Fund for Tuberculosis Research.

Read at the Fourth Congress of the International Association of Gerontology, Merano, Italy, July, 1957.

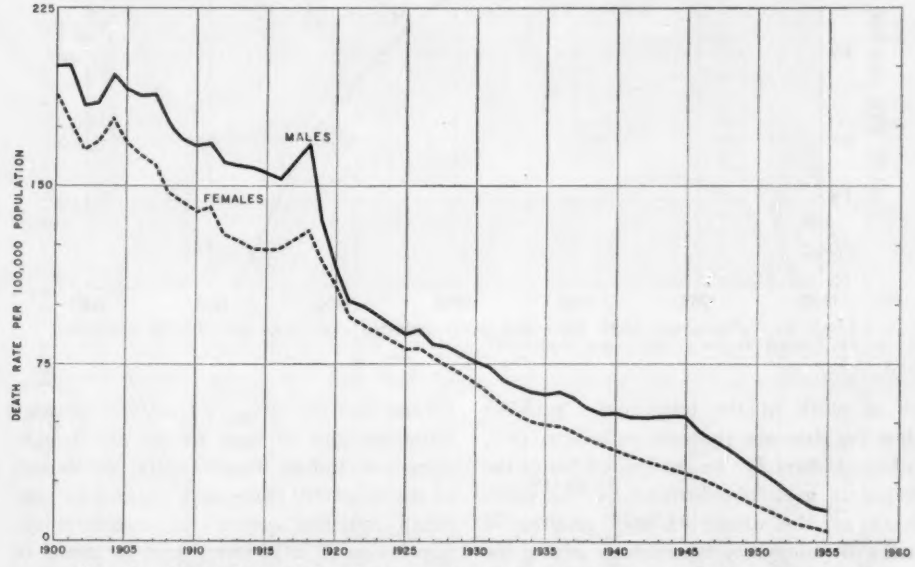


Chart 1.—Tuberculosis death rates among males and females in the United States in the years 1900-1955 (based on data for registration states prior to 1933. National Office of Vital Statistics).

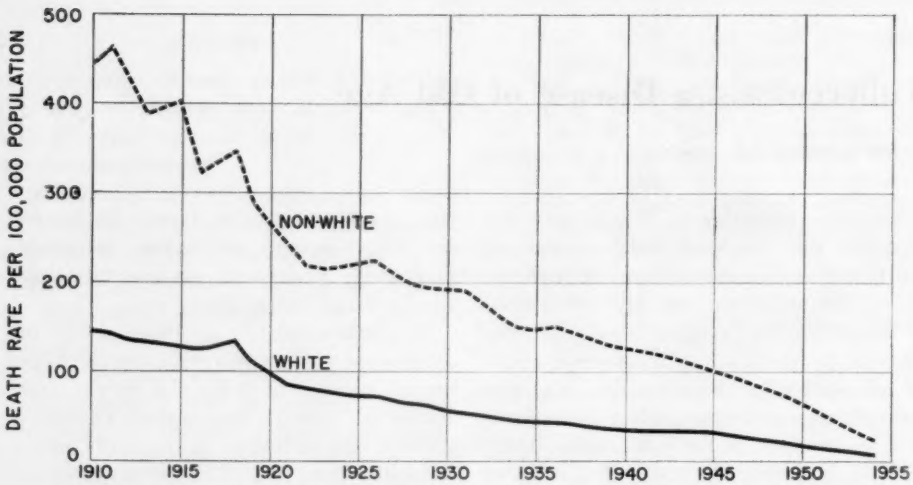


Chart 2.—Tuberculosis death rates among whites and nonwhites in the United States in the years 1910-1955.

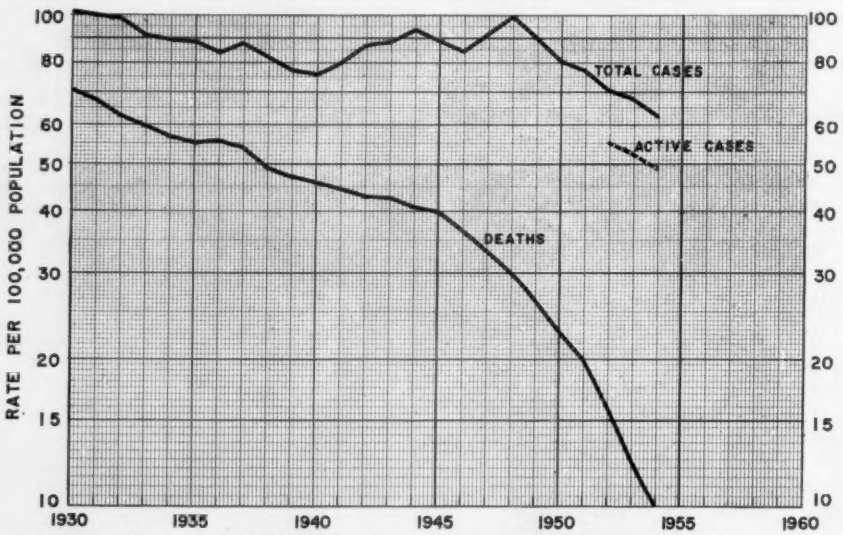


Chart 3.—Tuberculosis death rates and newly reported case rates per 100,000 population in the United States in the years 1930-1954.

are at work in the tuberculosis problem when the data are analyzed as to sex, race, and age (Chart 2). In the United States the picture is greatly influenced by the prevalence of the exudative and progressive forms of pulmonary tuberculosis among the nonwhite and immigrant elements of the population, chiefly the Negroes, the Puerto Ricans, and the refugees from war-tortured countries, and to some extent also by the American Indian. Undoubtedly, the decline of the mortality curve as it appears in published statistics conveys an overoptimistic impression if it is interpreted in terms of "cured" or "healed" tuberculosis. It is impossible to measure over a period of only a

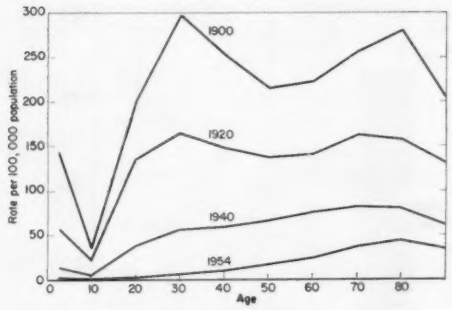


Chart 4.—Tuberculosis death rates by age in the United States in the years 1900-1954 (expanding death registration states).

few decades the true killing effect of a chronic disease if that disease in individual patients can outlast the period of recording. We know that the lower mortality is not the mere result of the decrease in the number of new active cases, which has fallen not nearly as much as the mortality (Chart 3). Therefore, it must be assumed that, especially during the past 10 years of chemotherapy, the swiftness of the decline of the mortality, at least in part, is not so much due to the number of persons cured of tuberculosis as to the increasing chronicity of the disease, which has shifted its weight into an older age group of the population. This change has become one of the most burning problems in tuberculosis care.

Tuberculosis used to be the greatest killer of mankind during the prime of life. The older generation of physicians has lived with that experience; the medical literature contains its proof, and in fiction the wasting of the young has tortured the imagination of authors and composers whose ranks have suffered the untimely loss from tuberculosis of Schiller and Stevenson, of Schubert and Chopin and many others. In the field of science, the study of tuberculosis itself has prematurely lost some of its greatest talents to the "white plague." Many of the great masters would enrich the world during a longer life had they been born into the present generation.

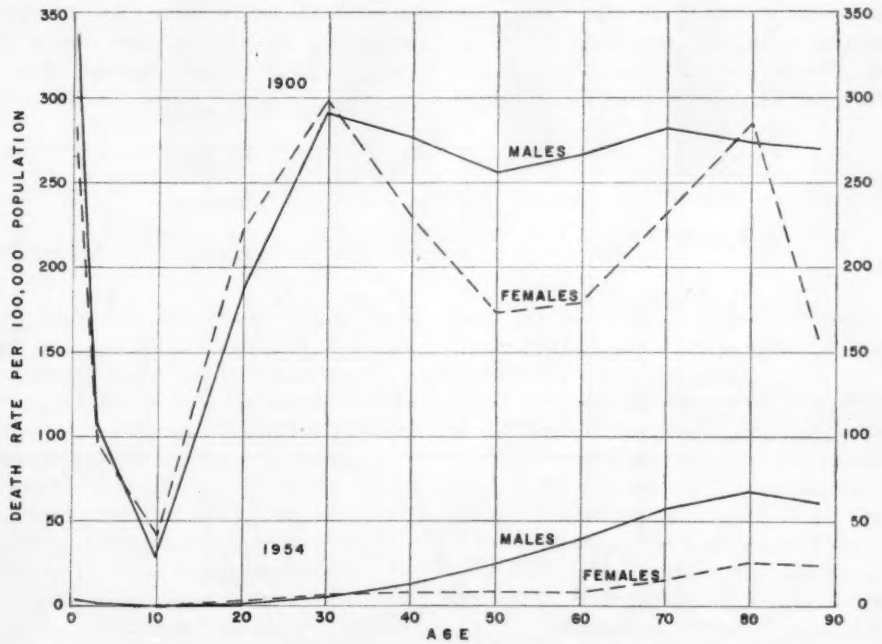


Chart 5.—Tuberculosis death rates by age among males and females in the United States in the years 1900 (death registration states, National Office of Vital Statistics) and 1954.

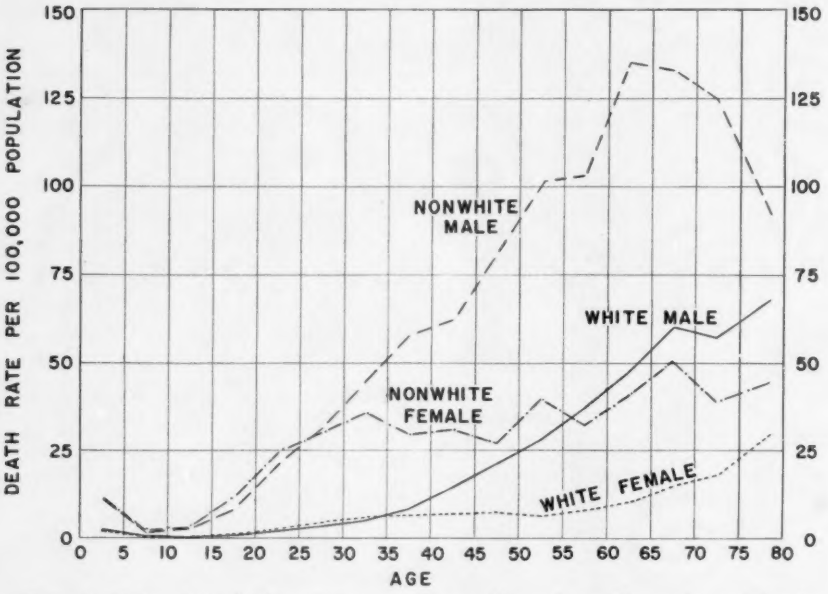


Chart 6.—Tuberculosis death rates by age among white and nonwhite males and females in the United States in 1953.

Beginning with the turn of the century, (Chart 4) the peak of the mortality during the second and third decades of life has flattened to comparatively insignificant values. The second peak, during the seventh decade of life, has decreased also but so much less that by now it has emerged as the highest elevation. While these changes apply to both sexes (Chart 5), the death rate among nonwhite females during the childbearing age still remains high. This is expressed in Chart 6, which also shows the

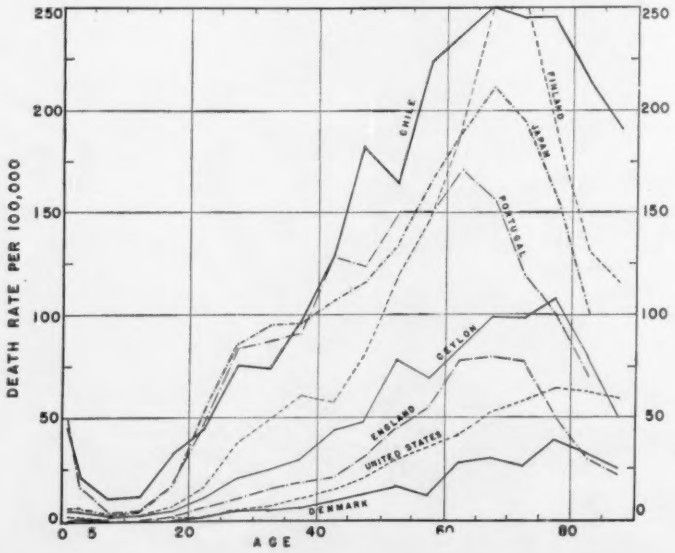


Chart 7.—Mortality from tuberculosis of respiratory system in certain countries in males in 1954.

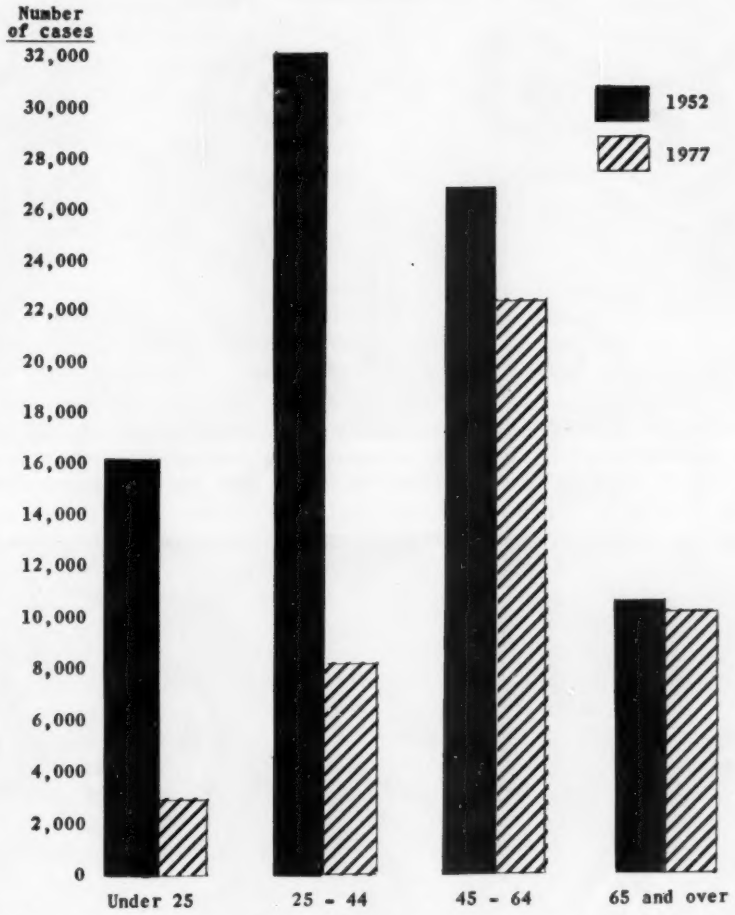


Chart 8.—Number of new active tuberculosis cases by age in the United States; 1953 actual and 1977 estimate.

great influence of the disease among nonwhite males on the total mortality; however, even among that most susceptible group of the population of the United States the mortality now reaches its highest elevation between the ages of 60 and 70 years.

Recently published reports of the World Health Organization contain the age distribution of deaths from tuberculosis in many European and non-European countries. In Chart 7 the figures from a selection of these countries are recorded graphically. While the total values differ widely, they show that the shift of the highest mortality to the senile age is universal; they also indicate the persistence of a high mortality among children in some countries.[1,2]

The National Tuberculosis Association, on the basis of recognized trends, has estimated the age distribution of new active cases of tuberculosis for 1977 in comparison with that of 1952 (Chart 8). This chart indicates that a decrease of almost 50% in the total number of such patients is expected but that the reduction will lessen in middle age groups and above the age of 65 will be almost nil. In 1952 a majority of about 11,000 new cases was found in people below

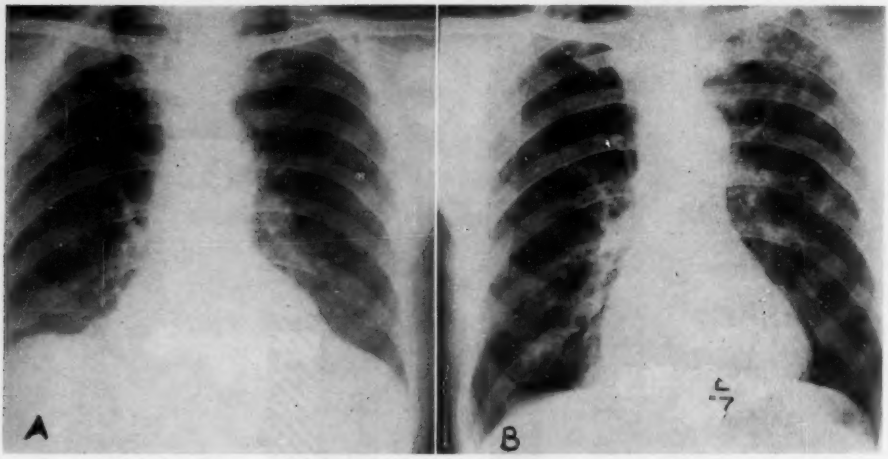


Fig. 1.—Male patient. *A*, at age 73, no demonstrable pulmonary involvement. *B*, four years later, exudative caseous tuberculosis involving the upper lobe of left lung. Sputum positive for tubercle bacilli.

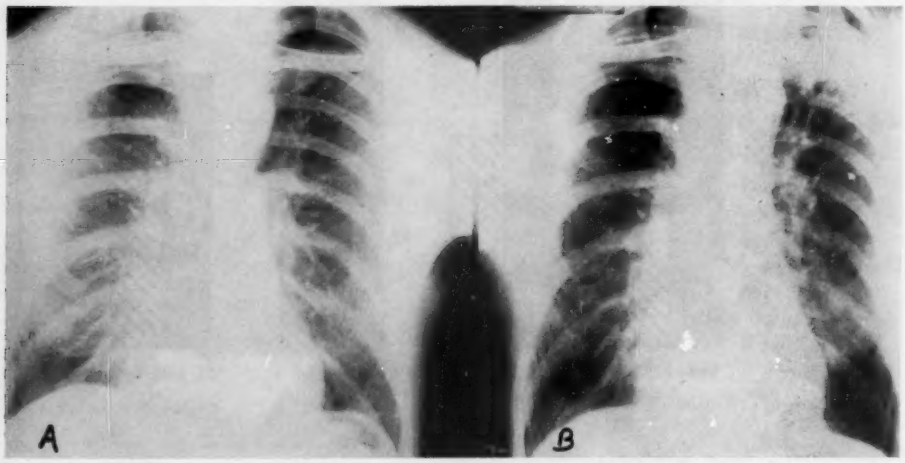


Fig. 2.—Male patient. *A*, at age 57, no demonstrable pulmonary involvement. *B*, two years later, pneumonic tuberculosis involving the upper lobe of the left lung. Sputum positive for tubercle bacilli.

the age of 45, in 1977 a majority of about 23,000 cases is expected to be found in people above that age.

In the past, the cirrhotic, the fibroid, and the fibrocaseous forms of pulmonary tuberculosis have been a rather uniform finding in elderly patients, who most always had been tuberculous for many years although the old disease was frequently associated with new bronchogenic exacerbations. In recent years, it has been a surprising and somewhat puzzling experience to find many fresh exudative involvements in patients where the absence of tuberculosis had been established when they were already in the old age group. The cases of two such patients are presented in Figures 1 and 2. The clinical-pathological picture of tuberculosis in the aged, therefore, differs less from that seen in young people than one should expect. There has been speculation that this type of senile disease might be due to the

fact that first infection with the tubercle bacillus occurs increasingly at a higher age than used to be the case and that a shorter period is available during which subsequently an adequate acquired immune resistance can develop. However, this consideration can hardly apply to the present-day senile patient whose childhood still fell into the period when primary infection occurred in the great majority of children. The likeliest explanation is that in previous generations, when roentgenologic examination was either not available or not applied widely, when the public as well as the medical mind associated tuberculosis essentially with the young, the disease was not expected and consequently not looked for in old persons. Its symptoms, if any, and eventually even death in many cases were attributed to nontuberculous causes.

Nowadays we find in the tuberculosis wards many patients who were hospitalized for some nontuberculous disease associated with tuberculosis. A few years ago the annual mortality report of one hospital listed 15 patients as having died of tuberculosis; it had been taken for granted that patients in the tuberculosis section must have died of that disease. A check of the records revealed that actually all 15 patients had died from nontuberculous involvements, 10 of them from malignant neoplasms. The true situation now is that the old tuberculous patient dies with rather than of tuberculosis. Often he has been sent to the tuberculosis wards for isolation rather than because of the symptoms of tuberculosis and the need for its treatment.

The question of the infectiousness of tuberculosis in some ways has become more complicated through modern chemotherapy rather than simplified. For practical considerations, we now must distinguish among three main groups of sputum findings; in the first group the sputum remains abundantly positive both on direct microscopic examination and on culture even under vigorous chemotherapy; in the second group, the production of bacilli is diminished to only occasional and scant positive results on culture; in the third group the sputum is completely negative on all tests by both direct miscroscopic examination and culture. The patients belonging to the first group cannot be permitted to return home to live with children and young adults even under the most favorable living conditions. Those in the second group are considered by many authors as practically noninfectious, and reports have been published indicating that they do not spread active disease and do not even lead to conversion of the response to tuberculin from negative to positive among persons living in their environment. One may not believe in the danger of occasional exposure to infection as a major factor in the distribution of tuberculosis, but the continuous contact in intimate home life has long proved itself as the essential cause of clinical disease. When the findings from routine roentgenologic examinations of the general population were compared with those in persons known to have lived in close contact with tuberculous individuals, it was found that the incidence of clinically important tuberculosis was three times as high in the latter group as among even the socially underprivileged of the general population.[3] Therefore, in spite of favorable reports to the contrary, extreme caution is indicated lest we send home grandparents to infect their grandchildren where in the past we often carelessly permitted parents to infect their children. This thought should apply even to the third group of patients, with negative sputum findings of seeming reliability. The fact that resected lesions from such patients yielded tubercle bacilli on either miscroscopic or cultural examination, or both, in well over one-third of all cases, offers much food for thought and caution.[4] As yet, we know too little about bacillary resistance to the antituberculous drugs and therefore about the permanence of negative sputum under chemotherapy even if that therapy is prolonged indefinitely after the patient's discharge from hospital care. Doubt also should prevail about the so-called openly healed cavity

which lately has been receiving so much attention in the literature.

Surgical resection of the most dangerously involved parts of the lung is now employed with impunity even in elderly patients, but as a group they are the least suitable for this form of therapy because of the high incidence of complicating factors which impair respiratory capacity and cardiac function.

The social, economic, and emotional problems of old age tuberculosis even overshadow the medical difficulties. The senile patient is lonely and wretched; often he has neither family nor friends; if he is widowed, his children, themselves beset by poverty, may not be able and at times are not willing to add to their burden by the small and larger ministrations by which they could show their affection and devotion. The old patient is frightened and helpless, and his reliance on social and welfare agencies is complete.

Since chemotherapy has come to the fore, the idea of home care for the tuberculous has received widespread attention. Unquestionably the period of hospitalization can now be shortened and treatment be continued at home, but home therapy without an initial stay in a hospital or sanatorium cannot be recommended. It is bound to fail in many aspects of diagnosis and therapy and deprives the patient of the indispensable education in the meaning and in the demands of his disease by having contact with other patients and being in the specifically created atmosphere of a tuberculosis hospital. When the time for discharge and home care approaches, the patient's social and economic situation often makes it hard or impossible for physicians and social workers to adjust the humane interpretation of the sweet word "home" to what in reality is awaiting the patient. A flat on the top floor of a cheap walk-up rooming house is not home, nor does a room for a whole family in slum quarters deserve that name. In brief, an address cannot be assumed to be a home before a thorough investigation has been made which appraises the home situation on the basis of high standards. Supervised rest and quiet, cleanliness, and comfort are still the mainstay in the treatment of tuberculosis. As yet, nobody has offered proof that the old methods can be replaced simply by the free provision of antibiotics by the community, even assuming that the drugs are taken as they were prescribed.

The closing of tuberculosis hospitals and sanatoria in reliance on modern chemotherapy is premature. They should serve as the desperately needed homes for homeless aged tuberculous patients, where they can enjoy a secure, dignified, and happy existence. Institutional care for tuberculosis in the sense of this altered interpretation of the term will develop more and more into a crying need as the disease increasingly becomes a geriatric problem.

Montefiore Hospital, Division of Pulmonary Diseases, 210th St. & Bainbridge Ave. (67).

REFERENCES

1. Epidemiological and Vital Statistics Report, World Health Organization, 1957, Vol. 10, No. 2, pp. 23-86.

2. Epidemiological and Vital Statistics Report, World Health Organization, 1957, Vol. 10, No. 4, pp. 149-218.

3. Bloch, R. G.; Francis, B. F.; Eisele, C. W., and Mason, E. W.: Roentgenological Group Examinations for Pulmonary Tuberculosis, Am. Rev. Tuberc. 37:174-199 (Feb.) 1938.

4. Bloch, R. G.; Buchberg, A. S.; Permutt, S., and Neumann, G.: The Bacteriology of Tuberculous Lesions Resected After Chemotherapy, Am. Rev. Tuberc. 77:245-259, Feb. 1958.

Sarcoidosis

Study of Twenty-Nine Cases, with a Review of Splenic, Hepatic, Mucous-Membrane, Retinal, and Joint Manifestations

MAJOR RICHARD H. FERGUSON (MC), and CAPT. JAIME PARIS (MC), U. S. A. F.

Since Hutchinson's [1] original description of the cutaneous manifestations of sarcoidosis, its systemic nature and protean symptomatology have been thoroughly documented. The more recent contributions have helped to clarify the history, epidemiology, and many clinical and pathologic aspects of the disease.[2-6]

The true incidence of sarcoidosis is unknown. The increasing routine use of thoracic roentgenograms in recent years has revealed many cases in apparently normal people; a considerable percentage of these persons have remained asymptomatic while the process spontaneously resolved. During World War II, sarcoidosis was discovered in 2.1 of each 100,000 inductees to the U. S. Army.[6] In the Swiss Army, Schönholzer [7] reported an incidence of 13 cases per 100,000 draftees. At Bellevue Hospital, 52 cases of sarcoidosis were seen in 10 years,[8] while the combined series of The Johns Hopkins Hospital and the Massachusetts General Hospital totaled 148 cases over a 20-year period.[5] At the Mayo Clinic, 194 cases of sarcoidosis were seen between 1940 and 1951.[9]

During a period of 29 months, we had an opportunity to study 29 cases of sarcoidosis on the Medical Service of the 7100th U. S. A. F. Hospital. These patients constituted 0.12% of the total hospital admissions for the same period. The striking frequency with which we encountered this disease and the occurrence of rather unusual manifestations in some patients prompted us to review our experience.

Submitted for publication July 30, 1957.

Present address of Capt. Paris: Section of Medicine, Mayo Clinic, Rochester, Minn.

Material and Methods

This study includes the cases diagnosed as sarcoidosis at the 7100th U. S. A. F. Hospital from January, 1955, through May, 1957. With the exception of two patients referred from neighboring Canadian Air Force bases, all the patients were U. S. Armed Forces personnel or their dependents engaged in overseas duty. Ten patients came to our attention because of abnormal findings on thoracic roentgenograms obtained for reasons unrelated to sarcoidosis. All patients were examined by one of us and were subjected to routine laboratory tests, estimation of the total proteins and albumin-globulin ratio, evaluation of tuberculin reactivity, and determination of serum calcium. When feasible, detailed ophthalmologic examination, roentgenograms of the hands, Kveim test, electrocardiogram, and skin tests with coccidioidin and histoplasmin also were obtained.

The diagnosis was made whenever the histologic appearance of material removed for biopsy showed noncaseating epithelioid tubercles compatible with sarcoidosis. In every case, acid-fast organisms were sought for in special stains of the histologic sections; in many instances, cultures were made from the resected tissues to exclude tuberculosis and mycoses. Clinical efforts also were made to rule out other diseases that could mimic the pathologic picture of sarcoidosis.

Results and Comment

Table 1 summarizes the pertinent clinical data in the 29 patients.

Michael and co-workers [6] reviewed experiences with sarcoidosis in World War II among U. S. military personnel and found that a preponderant number of 297 patients with histologically proved disease were from the South Atlantic or Gulf Coast states. The incidence in inductees from this region was 6.3 per 100,000, while the rate in those from the Middle Atlantic-Border states was 1.5 per 100,000 and that from the remainder of

TABLE 1.—*Clinical Data in Twenty-Nine Cases of Sarcoidosis*

Case (Admission Date)	Age, Yr.; Sex; Race; Home	History	Physical Findings	Roentgenologic Findings	Confirmation Biopsy	Course	Miscellaneous
1 (Jan., 1955)	20; M; N; S. C.	Bilateral blurred vision since Dec., 1954; anorexia, malaise, weight loss, cough, neg. chest x-ray April, 1954	Posterior cervical, axillary, inguinal adenopathy; bilat. uveitis	Massive bilat. hilar adenopathy; fine diffuse infiltration both lungs	Right scalene node	Continued smoldering uveitis; medical discharge from service June, 1955	Neg. blastomycin skin test
2 (Jan., 1955)	19; M; N; Va.	Productive cough and enlarged nodes for 2 mo.; neg. chest x-ray, 1954	Right supraclavicular, bilat. epitrochlear, inguinal adenopathy	Bilat. hilar adenopathy; general mottled infiltration both lungs; hand x-rays normal	Left epitrochlear node	Essentially asymptomatic; x-rays unchanged March, 1955; remained on active duty April, 1956	WBC 4/150
3 (Feb., 1955)	29; M; N; Ala.	Right nephrolithotomy, 1953; transient loss of vision left eye Dec., 1954; recent wt. loss, fever, effort dyspnea, cough	Right supraclavicular, left axillary bilat. inguinal adenopathy; bilat. uveitis; low-grade fever	Bilat. hilar adenopathy; patchy infiltration both lungs; hand x-rays normal	Right supraclavicular node	Uveitis improved with steroids but pulmonary infiltrates increased; resumption military duties June, 1955; passed left ureteral calculus Aug., 1956; eyes normal Aug., 1956	Blastomycin skin test neg.; sputum cultures neg. for TBC
4 (Feb., 1955)	37; F; W; Ariz.	Retrosternal discomfort, recent cough	None	Bilat. hilar adenopathy	Left scalene node	No follow-up	
5 (March, 1955)	28; F; N; La.	Enlarged epitrochlear nodes, 1950; intermittent nasal obstruction since 1951	General lymphadenopathy; small nodular lesions eyelid ear lobes, lips; granular mass left nares; neg. ophthalmologic exam.	Bilat. hilar adenopathy; cystic lesions carpal bones & right first metacarpal; clouding paranasal sinuses; normal skull x-rays	Mass left nares	Protracted nasal obstruction; hoarseness with gross involvement larynx in fall, 1956; both relieved by steroids; maintenance treatment required; anosmia since late 1956, unaffected by treatment; chest x-ray unchanged	Kveim pos.; normal ECG
6 (March, 1955)	31; M; W; Ont.	Red nodule left shin & swollen painful ankles March, 1955	Negative on entry	Bilat. hilar adenopathy	Right scalene node	Asymptomatic; returned to duty April, 1955	
7 (March, 1955)	30; M; W; Ohio	Low back pain, stiffness	None	Calcified granuloma left midlung periphery; bilat. hilar adenopathy; hand x-rays normal; arthritic changes sacroiliac joints	Right scalene node	Essentially asymptomatic with decrease in hilar adenopathy Dec., 1955; medical discharge from service because of rheumatoid spondylitis	
8 (April, 1955)	33; M; W; Texas	Recurring rheumatoid arthritis	Active arthritis of ankles; degenerative changes knees; minimal left supraclavicular adenopathy; neg. ophthalmologic exam.	Bilat. hilar adenopathy; minimal cystic phalangeal changes	Left supraclavicular node	Quiescent rheumatoid state; marked diminution hilar adenopathy Nov., 1955; essentially normal chest x-ray Nov., 1956	Normal ECG
9 (May 1955)	22; M; W; Ala.	Normal chest x-ray, 1954; wt. loss & substernal discomfort 1 mo.	Minimal posterior cervical & right axillary adenopathy	Bilat. hilar & right paratracheal adenopathy	Right scalene node	Asymptomatic; returned to duty June, 1955	Culture of node neg. for TBC

10 (June, 1955)	25; M; W; Wash., D. C.	Normal chest x-ray, 1953; asymptomatic; abnormal chest x-ray recent survey	None	Bilat. hilar adenopathy; patchy infiltrates both upper lungs; hand x-rays normal	Left scalene node	Asymptomatic; returned to duty June, 1955	Culture of node neg. for TBC
11	25; M; W; N. C.	Asymptomatic; abnormal routine premarital chest x-ray	None	Bilat. hilar adenopathy; hand x-rays normal	Right scalene node	Asymptomatic; returned to duty Oct., 1955	Culture of sputum neg. for TBC
12 (Nov., 1955)	26; M; N; Fla.	Cough, chest pain, hilar adenopathy, 1953; right thoracotomy, with diagnosis of sarcoidosis; asymptomatic since; referred for reevaluation	Minimal supraclavicular & posterior cervical adenopathy; right thoracotomy scar; neg. ophthalmologic exam.	Surgical deformity right 5th rib; pleural scarring on right; no renal calcification	Right hilar node & lung parenchyma	Asymptomatic Jan., 1957; coarse trabeculations distal phalanges on x-ray then	Normal ECG
13 (Nov., 1955)	21; M; W; Texas	Cough Oct., 1955; anemia, neutropenia, hepatosplenomegaly found at referring hospital	Posterior cervical & supraclavicular adenopathy bilat.; hepatosplenomegaly; neg. ophthalmologic exam.	Normal chest & hand x-rays	Left supraclavicular node	Progressive neutropenia & thrombocytopenia responding to cortisone; intercurrent meningitis July, 1956; hematologic relapse off cortisone; advent parenchymal infiltrate lungs Nov., 1956; splenectomy Dec., 1956; unexplained fever Feb. 1957	Focal granulomas on liver biopsy; normal ECG; L. E.-cell prep. neg.; bone marrow neg.; cultures of node neg. TBC and fungus; Kveim neg.
14 (Jan., 1956)	23; M; W; N. C.	Enlarged inguinal nodes, 1954, with diagnosis of sarcoidosis; recent conversion of tuberculin sensitivity	Pronounced bilat. inguinal adenopathy	Bilat. hilar & paratracheal adenopathy; hand x-rays normal	Left femoral node	Asymptomatic; discharged from service April, 1956	Culture of nodes neg. in 1955 & 1956 for TBC
15 (March, 1956)	24; M; W; La.	Routine chest x-rays normal Jan. 1956, abnormal March, 1956; no symptoms	None; neg. ophthalmologic exam.	Bilat. hilar adenopathy; mostly left; hand x-rays normal	Left hilar node	Asymptomatic; chest x-ray neg. Jan., 1957	Culture of nodes neg. for TBC and fungi; Kveim neg.; normal ECG
16 (May 1956)	30; M; W; Tenn.	Transient cervical adenopathy, 1955; chronic cough; normal chest x-ray Sept., 1955	None	Bilat. hilar adenopathy; hand x-rays normal	Right scalene node	Asymptomatic; decreased hilar adenopathy, advent of bilat. miliary infiltrates on chest x-ray Nov., 1956	Culture of node neg. for TBC
17 (June, 1956)	22; M; W; B. C.	Painful red nodule left shin Jan., 1956; transient blurred vision both eyes; swelling & pain of ankles; anorexia, left pleuritic pains, low-grade fever 1 mo.	None at this hospital; neg. ophthalmologic exam.	Bilat. hilar adenopathy & patchy parenchymal infiltrates; hand x-rays normal	Right scalene node	Asymptomatic; lung parenchyma unchanged but hilar adenopathy decreased 3 wk. after entry; chest x-ray normal Sept., 1956	L. C.-cell preparation neg.; normal ECG; cultures of node neg. for TBC, fungus and Brucella
18 (June, 1956)	20; M; N; Va.	Blurring vision, tearing, photophobia; hacking, recent cough	Bilat. uveitis with secondary glaucoma; right massive supraclavicular adenopathy; multiple subcut. nodules upper arms	Bilat. hilar adenopathy; finely mottled infiltrates both lungs; hand x-rays normal	Right supraclavicular node	Respiratory insufficiency & fever treated with cortisone elsewhere Dec., 1956; asymptomatic, chest x-ray unchanged, uveitis inactive Feb., 1957	Kveim pos.; normal ECG; Brucella agglutination neg.; node and gastric cultures neg. for TBC
19 (July, 1956)	21; M; N; Tenn.	Protracted fever and nonspecific hepatitis, 1954; recent fever, jaundice, pruritus, cough, weight loss, effort dyspnea, night sweats	Scleral icterus, fever, hepatosplenomegaly; neg. ophthalmologic exam.	Bilat. midlung infiltrates; cystic phalangeal changes	Liver biopsy	Progressive obstructive jaundice, greatly improved by cortisone; maintenance doses needed; status unchanged March, 1957	Kveim neg.; normal ECG; increased alkaline phosphatase

TABLE 1.—*Clinical Data in Twenty-Nine Cases of Sarcoidosis*—Continued

Case (Admission Date)	Age, Yr.; Sex; Race; Home	History	Physical Findings	Roentgenologic Findings	Confirmation Biopsy	Course	Miscellaneous
20 (July, 1956)	25; M; W; Ariz.	Normal chest x-ray Nov., 1955; asymptomatic; abnormal chest x-ray on discharge physical	Small right supraclavicular node	Finely mottled infiltrates right midlung field; hand x-rays normal	Right supraclavicular node	Asymptomatic; x-rays unchanged Oct., 1956	Culture gastric contents & node neg. for TBC & fungus
21 (Aug., 1956)	20; M; N; N. C.	Normal chest x-ray Nov., 1955; cough, wheezing, abnormal chest x-ray June, 1956	Bilat. axillary supraclavicular adenopathy; bilat. wheezes and bronchi; inspiratory stridor with suprasternal retraction; neg. ophthalmologic exam.	Bilat. patchy nodular pulmonary infiltrates; minimal hilar adenopathy; hand x-rays normal	Right supraclavicular node	Persistent mild respiratory symptoms; chest x-ray unchanged Dec., 1956	Vital capacity, 60% normal; prominent R wave in V_1; neg. bronchoscopy; pos. Kveim; culture of node neg. for TBC & fungi
22 (Sept., 1956)	18; M; N; Va.	Normal chest x-ray July, 1955; enlarged nodes in neck recently	General lymphadenopathy	Diffuse hazy pulmonary infiltrates; bilat. hilar & paratracheal adenopathy; cystic changes carpal bone	Left cervical node	Progressive peripheral adenopathy; hoarseness with laryngeal edema; appearance of retinal granulomas; clearing of pulmonary parenchymal infiltrates; left uveitis Feb., 1957	Pos. Kveim; normal ECG; culture of nodes neg. for TBC & fungi
23 (Nov., 1956)	24; M; W; Ky.	Asymptomatic; abnormal chest x-ray on discharge physical	Right supraclavicular & axillary adenopathy; neg. ophthalmologic exam.	Bilat. mottled pulmonary infiltrates; minimal hilar adenopathy; cystic changes carpal bone	Right supraclavicular node	Asymptomatic; discharged Dec., 1956	Normal ECG; culture of node neg. for TBC
24 (March, 1957)	21; M; W; N. C.	Asymptomatic; abnormal chest x-ray on discharge physical	None; neg. ophthalmologic exam.	Bilat. hilar adenopathy; hazy infiltrate rt. apex; hand x-rays normal	Left scalene node	Asymptomatic; discharged May, 1957	Kveim pos.; liver biopsy normal; gastric cultures neg. for TBC
25 (March, 1957)	23; M; N; S. C.	Asymptomatic; routine chest x-ray abnormal	Rt. axillary adenopathy; neg. ophthalmologic exam.	Bilat. hilar & rt. paratracheal adenopathy; miliary pulmonary infiltrate with confluent patches rt. upper; hand x-rays normal	Left lung biopsy	Asymptomatic; discharged June, 1957	Gastric & tissue cultures neg. for TBC and fungi; liver biopsy neg.; Kveim pos.; nodes from rt. & lt. scalene & rt. axilla neg.; ECG normal
26 (April, 1957)	28; F; W; Texas	Effort dyspnea; lost 10 lb.; night sweats, chest tightness several months	None; neg. ophthalmologic exam	Patchy infiltrates both upper lung fields; hand x-rays normal	Left lung biopsy	Minimal effort dyspnea on discharge May, 1957	Rt. scalene node neg.; ECG normal; vital capacity 60% normal; culture tissue & sputum for TBC & fungi neg.
27 (May, 1957)	23; M; N; Fla.	Asymptomatic; routine chest x-ray abnormal	Small cervical, axillary, rt. epitrochlear adenopathy; neg. ophthalmologic exam.	Bilat. hilar adenopathy; patchy infiltrates both upper & midlung fields; hand x-rays normal	Right epitrochlear node	Asymptomatic; discharged June, 1957	Kveim pos.; ECG normal; gastric cultures for TBC & fungi neg.
28 (May, 1957)	23; M; N; Ga.	"Lumps" on arms, recurrent eye pain with blurring and photophobia, loss of 16 lb. over 3-mo. period	Subcutaneous nodules 3-8 mm. upper arms and thighs; spleen palpable; small cervical & rt. epitrochlear adenopathy; bilat. uveitis	Bilat. hilar & rt. paratracheal adenopathy; diffuse miliary parenchymal infiltrates; hand x-rays normal	Right epitrochlear node	Ocular symptoms cleared with topical hydrocortisone; discharged June, 1957	Kveim pos.; normal ECG
29 (May, 1957)	23; M; N; Ark.	Cough March, 1957; arthritis wrists, ankles, knees April, 1957; fever, night sweats	Wrists, knees, ankles swollen, warm, tender; rt. epitrochlear nodes palpable; neg. ophthalmologic exam.	Bilat. hilar & paratracheal adenopathy; miliary infiltrates both lungs; hand x-rays normal	Right scalene node	Daily intermittent fever 101 F; arthritis gradually cleared in June, 1957; transferred to U. S. July, 1957, with chronic fever	Kveim pos.; normal ECG; L. E.-cell preparation neg.; antistreptolysin titer 12-50 units; blood cultures neg. Gastric cultures for TBC neg.

the country was only 0.7 per 100,000. On the other hand, Carr and Gage [9] found that 177 patients with sarcoidosis at the Mayo Clinic had a geographic distribution that paralleled that of the total clinic registration. No regional predilection could be discerned even when their data were corrected so that they corresponded to those of the military personnel studied by Michael's group insofar as age, sex, race, and severity of disease were concerned.

Twenty-four of our twenty-nine patients were from the southern United States, and twenty of these were from coastal states. Table 2 shows the regional distribution of the permanent residences of the patients with sarcoidosis compared with that of the total hospital population. Unfortunately, we do not have data that can be analyzed as to birthplace, duration of residence, or exposure to a rural environment.

It has been recognized for a long time that Negroes are particularly prone to have sarcoidosis. Cummings and associates [10] studied 1194 Veterans' Administration cases and found that the hospitalization rate for sarcoidosis in World War II veterans was 3.3 per 100,000 in white persons and 40.1 per 100,000 in Negroes. This ratio of 12:1 in the incidence rates was less than the 18:1 ratio in the 297 cases of the Army series reported by Michael's group.[6] The relative incidence between the races in the latter work was fairly constant in all sections of the country. The racial predilection in our small group is roughly comparable to the findings just given. Thus, the rate of sarcoidosis was calculated to be 876 per 100,000 Negroes admitted to the hospital, while the rate for white patients was 70.1 per 100,000 admitted to the hospital, which gives a ratio of 12.5:1.

TABLE 2.—*Geographic Distribution of Permanent Residences of Twenty-Nine Patients with Sarcoidosis*

Geographic Location *	Patients		Total Hospital Registration, %
	No.	%	
New England States	0	0	6.1
Middle Atlantic States	0	0	18.8
South Atlantic States	13	45	15.2
East North Central States	1	3	16.8
West North Central States	0	0	10.0
East South Central States	5	17	8.0
West South Central States	6	21	11.6
Mountain States	2	7	3.9
Pacific States	0	0	8.2
Canada	2	7	1.4

* New England—Me., N. H., Vt., Mass., R. I., Conn.; Middle Atlantic—N. Y., N. J., Pa.; South Atlantic—Del., Md., D. C., Va., W. Va., N. C., S. C., Ga., Fla.; East North Central—Ohio, Ind., Ill., Mich., Wis.; West North Central—Minn., Ia., Mo., N. D., S. D., Neb., Kan.; East South Central—Ky., Tenn., Ala., Miss.; West South Central—Ark., La., Okla., Tex.; Mountain—Mont., Ida., Wyo., Colo., N. Mex., Ariz., Utah, Nev.; Pacific—Wash., Ore., Calif.

As already indicated, at least 10 of our 29 patients had no symptoms relevant to sarcoidosis during our period of observation, and their disease probably would not have come to medical attention except as a result of incidental thoracic roentgenograms. Several other patients in whom the disease was detected because of routine thoracic roentgenograms had complaints presumably due to sarcoidosis that had been too trivial to cause them to report to a physician.

This incidence of asymptomatic patients is greater than was encountered by McCort and associates [11] and by Ricker and Clark [4] in similar military populations; these workers found that asymptomatic patients constituted 21% and 14% of their respective series. On the other hand, 39% of Moyer and Ackerman's [12] patients were without significant complaints.

Table 3 summarizes the frequency of symptoms encountered in our series, with the incidence of involved organs as determined clinically.

The reaction to the intradermal tuberculin test (second-strength purified protein derivative) was originally negative in 25 of the 29 patients. One year later, two of the nonreactors had become sensitive to tuberculin. One of these two patients (Case 8) had undergone complete resolution of his hilar adenopathy at the time the reaction became positive, and evidence of sarcoidosis or tuberculosis could not be found. The second patient (Case 14) had unchanged inguinal adenopathy when his reaction became positive. A third biopsy of a lymph node then confirmed the diagnosis of sarcoidosis, with negative results for tubercle bacilli on culture and guinea pig inoculation.

TABLE 3.—*Symptoms and Organs Involved Clinically in Twenty-Nine Patients with Sarcoidosis*

Symptoms	Patients	Organs Involved	Patients
Cough	10	Mediastinal lymph nodes	24
Blurred vision	6	Peripheral lymph nodes	18
Loss of weight	6	Pulmonary parenchyma	19
Fever	5	Bones	5
Dyspnea	5	Uveal tract	5
Enlarged lymph nodes	4	Spleen	3
Thoracic discomfort	4	Skin and subcut. tissue	3
Arthritis	3	Joints	3
Erythema nodosum	2	Liver	2
Hoarseness	2	Ocular fundus	1
Nasal obstruction	1	Nasal mucosa	1
Itching & jaundice	1	Larynx and epiglottis	1

We had no means of knowing whether the appearance of the positive reaction to tuberculin heralded an initial tuberculous infection in these patients or merely represented the termination of a transient anergic state acquired during active sarcoidosis.

Nineteen of twenty patients tested with histoplasmin had negative results. Only 2 of the 20 tested with coccidioidin had positive reactions (Cases 1 and 21). Sones and Israel [13] have studied the altered immunologic reactivity of patients with sarcoidosis and demonstrated a greatly decreased incidence of positive responses to many cutaneous antigens besides tuberculin.

The literature contains conflicting reports as to the specificity and diagnostic value of the Kveim test.[14-16] Perhaps some of this variation of opinion stems from the unavoidable differences in the antigenic quality of the tissue used as the source of test material plus lack of standardization in its preparation. Most workers consider that the test gives positive results when the disease is active.

Dr. Kenneth Burdick, our dermatologic consultant, administered the Kveim antigen to 12 of our patients and observed typical positive reactions in 9; biopsy of the induced papules was done in 8 of these 9 patients. Of the three patients who had negative reactions, one (Case 15) had clinically inactive disease, while the other two (Cases 13 and 19) were chronically ill with progressive sarcoidosis. The last-named patient was receiving cortisone when the Kveim test was done. We observed the disappearance of a positive Kveim papule in Case 5 after two weeks of steroid therapy.

Abnormalities in values for total serum protein were surprisingly rare, only one patient having values consistently greater than 8 gm. per 100 ml. Seven patients had values for serum globulin more than 3 gm. per 100 ml., which is the upper limit of normal in our laboratory; the values in another two were intermittently increased.

An increase in blood calcium was encountered in only one patient, and observations on two subsequent occasions revealed normal values.

Changes in leukocyte counts and in percentages of eosinophils and monocytes were not significant. The leukocyte count was less than 4000 cells per cubic millimeter of blood in one instance and between 4000 and 5000 on occasions in another six. The values for eosinophils were rather variable and were more often zero than they were greater than 3%. In only three patients were the eosinophils increased on all occasions. Monocytosis was not present in any patient, and only one patient (Case 13) had significant anemia.

The corrected erythrocytic sedimentation rate (Wintrobe method) was greater than 10 mm. during the first hour in men or 15 mm. in women in 13 patients. Nine of the remaining 15 patients on whom data were available were asymptomatic patients whose diagnoses were based on routine thoracic roentgenograms. There appeared to be a fair correlation between the degree of clinical activity and the sedimentation rate.

In general, the results of chemical studies on the blood and hematologic procedures were not helpful in suggesting or confirming the diagnosis in our group of patients.

Biopsy of the scalene fat pad was by far the most useful diagnostic tool in our hands when intrathoracic involvement was found without enlargement of peripheral lymph nodes. Eleven of nineteen patients who underwent supraclavicular exploration on one or both sides had scalene nodes with his-

tologic evidence of sarcoidosis. This is comparable to the experience reported by Hodgson and Woolner,[17] in which scalene dissection established the diagnosis of sarcoidosis in 50% of such cases. Consideration of diagnostic thoracotomy was averted in at least eight of our patients by positive results of biopsy of scalene nodes.

All 11 of the patients with diagnostic scalene nodes had hilar adenopathy; 4 of them also showed some pulmonary parenchymal involvement. Ten of the eleven did not exhibit any significant peripheral adenopathy. In Cases 2, 10, 15, 19, 24, 25, and 26, results of biopsy of scalene nodes initially were negative and the diagnosis was established subsequently by thoracotomy, biopsy of the liver, or supraclavicular exploration on the opposite side.

The absence of enlarged peripheral lymph nodes in 11 of our patients is not in keeping with the experience of other observers. Longcope and Freiman[5] concluded that superficial nodes were enlarged during some phase of the disease in virtually all cases. This was true in 26 of the 28 cases in McCort's[11] group, in all of Reisner's[3] 35 cases, and in all of Riley's[8] 52 cases. Perhaps the difference in our experience resulted from the discovery of the disease in an early phase and the brief period of observation in some patients. The fact that 5 of the 10 asymptomatic patients did not have peripheral adenopathy tends to support this hypothesis.

During the years 1955 and 1956 biopsy of peripheral lymph nodes was done in our hospital in 50 cases in which the diagnosis was indeterminate. Table 4 shows the histologic diagnosis on the tissue resected and the final clinical diagnosis in all instances. It will be noted that the pathologist's impression of sarcoidosis was proved erroneous on one occasion when cultures of the node yielded tubercle bacilli. This patient had had isolated supraclavicular adenopathy for a long time, with no other clinical findings except a strongly positive reaction to tuberculin. In two of the three patients in whom

TABLE 4.—*Final Diagnoses in Fifty "Indeterminate" Cases in Which Biopsy Was Done*

Cases	Histologic Diagnosis	Final Clinical Diagnosis	No.
20	Sarcoidosis	Sarcoidosis	19
		Tuberculosis	1
14	Reactive hyperplasia	Undetermined	12
		Bronchogenic carcinoma	1 *
		Myelogenous leukemia	1 †
5	Lymphoma	Lymphoma	
3	Normal lymphoid tissue	Undifferentiated mediastinal carcinoma	1 *
		Sarcoidosis	2 ‡
2	Tuberculosis	Tuberculosis	
2	Normal supraclavicular fat pad	Sarcoidosis	*§
2	Metastatic carcinoma	Metastatic carcinoma	
2	Atrophic lymphoid time	Undetermined	

* Thoracotomy.
† Bone-marrow aspiration.
‡ Not included in this series for lack of histologic confirmation.
§ Liver biopsy

normal lymphoid tissue was found, the most likely final clinical diagnosis was thought to be sarcoidosis, although these patients are not included in this series for lack of histologic confirmation. It is evident that, in our material, sarcoidosis is by far the commonest cause of lymphadenopathy requiring biopsy.

Unusual Manifestations

Five of our twenty-nine patients exhibited rather unusual manifestations of sarcoidosis. Involvement of the spleen, liver, mucous membranes, ocular fundus, or joints was demonstrated.

Spleen.—Splenic involvement in sarcoidosis as manifested by palpable enlargement has been recorded in 19% of a collected series, while necropsy studies revealed the spleens to be affected in 50% of 138 cases.[18] Despite this, it is unusual for major ill effects to arise from the spleen in sarcoidosis. Splenectomy has not effected a change in the course of sarcoidosis in other organs but has aided materially in the control of certain hematologic complications.

Anemia is not common in sarcoidosis. Nonhemolytic anemia has been described in association with other manifestations of hypersplenism on several occasions and has responded to splenectomy. A few instances of isolated frank hemolytic anemia in the presence of sarcoidosis have been reported.[11,19-21] Splenectomy in three of these reported cases did not prevent further

hemolytic activity; two of these three spleens did not reveal sarcoidosis, and the diagnosis was established from tissue removed from other sites. The relationship of the spleen to this type of anemia is open to question, and experience thus far suggests that splenectomy is of dubious value.

Thrombocytopenia in sarcoidosis has been found alone and in conjunction with nonhemolytic anemia and leukopenia. These cytopenias, singly or in combination, are usually associated with large spleens containing sarcoid granulomas and are relieved by splenectomy. This syndrome of hypersplenism has no apparent hematologic differentiation from that secondary to such conditions as congestive splenomegaly, Gaucher's disease, and splenic lymphoma. The mechanism by which the spleen exerts a cytopenic action in sarcoidosis has not been elucidated, but most authors have not seen evidence of increased splenic phagocytosis. Several have described megakaryocytic hyperplasia in the bone marrow, with failure of platelet production.

Thrombocytopenia has been the most ominous feature in the reported cases of hypersplenism associated with sarcoidosis. At least 16 patients with decreased platelet counts have been recorded,[20,22-35] of whom 4 died as the result of a bleeding diathesis. Ten of the sixteen were subjected to splenectomy because of thrombocytopenia; the experience in these has been encouraging, with nine patients cured and one immediate postoperative death. The case of Edwards and co-workers[33] demonstrated that a fulminating hemorrhagic course may terminate fatally before splenectomy can even be attempted.

Splenectomy in several other cases has relieved anemia and leukopenia not associated with depression of platelets. Such patients often have been subjected to operation primarily because of symptoms due to massive splenic enlargement rather than to the hematologic changes.

One of our cases illustrated the changes of hypersplenism and the response to cortisone and splenectomy.

CASE 13.—A 21-year-old white man was referred to us in October, 1955, after an acute respiratory infection. Supraclavicular adenopathy and hepatosplenomegaly had been encountered elsewhere, with a value for hemoglobin of 8.0 gm. per 100 ml. and a leukocyte count of 3250 cells per cubic millimeter of blood, with 70% lymphocytes. The history revealed no known exposure to toxic agents and no prior hematologic disorder.

Studies disclosed normal smears of peripheral blood and bone marrow except for basophilic stippling, macrocytosis, and polychromasia in the erythrocytes. Results of a large battery of other laboratory tests were normal.

Needle biopsy of the liver showed nonspecific focal granulomatous lesions in the portal triads. A palpable supraclavicular node was normal on biopsy. By mid-November, the hemoglobin had spontaneously increased to 15.5 gm. and the leukocyte count was 7000, with 50% lymphocytes.

In January, 1956, the patient returned for follow-up studies. A second lymph node biopsy from the left supraclavicular zone revealed changes compatible with sarcoidosis. Cultures of the tissue and of gastric contents were negative for acid-fast bacilli and fungi. Skin reactions to coccidioidin, histoplasmin, and tuberculin were negative. L. E.-cell preparations were repeatedly normal.

By April, 1956, the volume of packed erythrocytes (hematocrit) had decreased to 37% and the neutrophilic granulocytes, to 30%. The platelet count was 130,000. Cortisone, 50 mg. daily in divided doses, was given for two months with no apparent effect on the blood values or physical findings.

By June, 1956, the platelets were ranging from 52,000 to 78,000. Bleeding time, clot-retraction time, and results of the tourniquet test remained normal. The dose of cortisone was increased to 50 mg. every six hours. Within two weeks, the platelet count increased to 149,000 and the spleen was no longer palpable. In mid-July, acute meningitis developed, with a cerebrospinal fluid cell count of 2370, containing 85% lymphocytes. The cerebrospinal fluid sugar was 29 mg. per 100 ml., and the protein was 136 mg.; the value for chloride was 113 mEq. per liter. Stain and culture of the fluid showed no bacterial pathogens or fungi. A presumptive diagnosis of tuberculous meningitis was made despite the negative tuberculin reaction, and therapy with isoniazid, streptomycin, and aminosalicylic acid was started. After 10 days, meningeal signs and fever abated and the lesions of herpes zoster appeared in the right fifth and sixth thoracic segments. Use of cortisone was

discontinued on Aug. 11, but antituberculotic therapy was maintained. By November, the spleen, liver, and cervical nodes had enlarged to their previous dimensions and, for the first time, a diffuse miliary infiltrate appeared in both lungs. The platelets decreased to 86,000 and subsequently to 54,000. The hemoglobin was 11.0 gm., with a hematocrit of 34%, and the leukocyte count was 6,950, with 15% neutrophilic granulocytes. A Kveim test gave a negative reaction.

At this juncture, splenectomy was decided on, and preoperative therapy with cortisone, 75 mg. daily, was given for two weeks prior to operation. During this interval, the neutrophil and platelet counts increased, while the spleen receded in size from 5 cm. to 2 cm. below the left costal margin.

In December, 1956, the spleen was removed by Dr. Philip Cox through a left transthoracic approach. The left lung was observed to be seeded with miliary infiltrates. The spleen weighed 780 gm. and was studded with nodules histologically typical of sarcoidosis. Antituberculotic medication was continued, but the use of cortisone was stopped postoperatively. Blood values have been normal since then except for persistent leukocyte counts in the neighborhood of 14,000, with approximately 67% lymphocytes.

Early in February, 1957, an unexplained intermittent fever, with temperature ranging up to 104 F, appeared and persisted for two weeks. Multiple enlarged nodes in both axillae were also present, but other objective changes could not be found. Thorough investigation revealed no cause for the fever other than active sarcoidosis.

This case had several notable features. The meningeal reaction remained unexplained; sarcoidosis did not appear likely as the etiologic factor in view of the abrupt onset while large doses of cortisone were being given. Intercurrent herpes zoster or infection with some other virus would have been an attractive hypothesis had it not been for the reduced sugar in the cerebrospinal fluid. For these reasons, we felt compelled to treat the patient as a presumptive case of tuberculous meningitis. The subsequent failure to isolate acid-fast organisms and the persistence of a negative reaction to tuberculin make complicating tuberculosis appear unlikely in retrospect.

The leukocyte count increased from 3000 to 14,000 during the period of observation, but the percentage of neutrophilic granulocytes remained consistently depressed except when large doses of cortisone were being given. The failure of splenectomy to alter the relative neutropenia was surprising. This is contrary to all previous reports of sarcoid hypersplenism that we have read.

Liver.—Histologic involvement of the liver in sarcoidosis has been reported in 67% of 138 necropsies [18] and in 78% of 73 clinically proved or suspected cases of the disease by hepatic biopsy.[36] Severe hepatic dysfunction occurs with much less frequency. Analyzing the clinical data in 710 reported cases of sarcoidosis, Branson and Park [18] found hepatomegaly in 125 cases, clinical involvement of the liver in 50, a total serum bilirubin greater than 1 mg. per 100 ml. in 22, and frank jaundice in 13. However, only three of the icteric patients had histologic confirmation of hepatic involvement. Death from hepatic sarcoidosis has been reported only twice in the English literature.[18,37]

The basic pathologic picture in hepatic sarcoidosis consists of infiltration of the hepatic parenchyma with epithelioid granulomas. The architecture of the hepatic lobe remains relatively undisturbed, and few changes are found in the cells. When cirrhosis occurs, it probably results from healing of the granulomas. Klatskin and Yesner [38] emphasized the fact that epithelioid granulomas can be superimposed on other diseases, such as infectious hepatitis, Laennec's cirrhosis, and cirrhosis secondary to arsenical poisoning. That hepatic granulomas by themselves are not diagnostic of sarcoidosis was further stressed by Klatskin and Yesner's review of 650 hepatic biopsies, 29 of which showed granulomas compatible with Boeck's sarcoid. Of these, 15 cases were proved to be sarcoidosis; 7 were due to tuberculosis; 2 were caused by erythema nodosum; 1, by a mycotic infection; 1, by brucellosis, and 3 by "viral infections."

Derangement in hepatic function is found in a substantial number of patients with sarcoidosis. Of 581 patients whose records were reviewed by Branson and Park,[18] 14% were found to have abnormal results of one or more liver-function tests, not including

abnormal serum proteins or postive findings on liver biopsy. When values for serum globulin of 2.75 gm. or more were included as an index of hepatic dysfunction, this incidence increased to 61%.

Shay and associates [36] made a systematic study of hepatic function in 24 patients who had proved sarcoidosis. Values for serum bilirubin greater than 1.5 mg. per 100 ml. were found in only one patient, who eventually was shown to have a hemocholecyst, with a blood clot filling the cystic and common bile ducts. Increased thymol turbidity was found in 13 cases; abnormal serum colloidal gold reactions, in 16; abnormal cephalin-cholesterol flocculation reactions, in 10; increased zinc sulfate turbidity, in 21, and abnormal retention of sulfobromophthalein, in 10. Thirteen of these patients had determinations of serum proteins by electrophoresis; ten patients were clinically "active" and had reductions in albumin and α_1-globulin along with concomitant increases in γ-globulin, whereas three "cured" patients showed essentially normal values. Increments in γ-globulin were closely paralleled by increases in zinc sulfate turbidity.

Only six detailed case reports of sarcoidosis with predominent hepatic involvement have been found by us in the English literature. Mino and co-workers [39] reported on a 26-year-old Negro woman with sarcoidosis who had involvement of the skin, lymphatics, lungs, liver, spleen, pancreas, and possibly the spinal cord and heart. The patient had exertional dyspnea and ascites in conjunction with moderate anemia, hypoprothrombinemia, retention of sulfobromophthalein, a 4+ cephalin-cholesterol flocculation reaction, and reversal of the albumin-globulin ratio. Laparotomy disclosed pronounced enlargement of the liver and spleen, with associated portal hypertension. Establishment of a splenorenal shunt resulted in considerable clinical improvement and complete disappearance of the ascites. The spleen and liver showed microscopic evidence of sarcoidosis. The hepatic lesions were found primarily about the tributaries of the portal vein in many portal triads. The central lobular veins showed occasional involvement, and several of the larger apparently sublobular veins contained striking infiltration of the walls.

Case 5 in Klatskin and Yesner's [38] series of 15 cases of proved hepatic sarcoidosis concerned an 11-year-old Negro girl who had a 10-month history of anorexia, abdominal pain, nausea, vomiting, cough, dyspnea, and high fever. She presented hepatosplenomegaly, peripheral adenopathy, and jaundice. An increase in alkaline phosphatase had preceded the onset of jaundice by five months. Leukopenia, mild anemia, increased plasma proteins with reversal of the albumin-globulin ratio, a total serum bilirubin of 3.99 mg. with an increased direct-reacting fraction, elevated thymol turbidity, retention of sulfobromophthalein, and a prolonged prothrombin time were found. Biopsy of the liver showed extreme infiltration of the portal and intralobular zones by typical lesions of sarcoidosis along with connective-tissue proliferation in the portal zones.

Longcope and Freiman [5] reported on a 29-year-old Negro woman with involvement of the skin, lungs, and lymph nodes who was observed for two years because of intermittent high fever, ascites, edema of the extremities, and severe hepatomegaly. Findings on biopsy of the liver were compatible with sarcoidosis. She had moderate anemia, reversal of the albumin-globulin ratio, and increased alkaline phosphatase. At necropsy, the liver showed cirrhosis with both early and healing sarcoids in the periportal regions. The finding of fibrocaseous and cavitary pulmonary tuberculosis in this case casts some doubt on the diagnosis of sarcoidosis.

Wagoner and associates [40] reported the case of a 25-year-old Negro man with jaundice of 30 months' duration, hepatosplenomegaly, and one episode of unexplained fever. Thymol and zinc sulfate turbidities, serum lipides, alkaline phosphatase, and total proteins were persistently increased,

along with an initial reversal of the albumin-globulin ratio. Serial biopsy of the liver disclosed diffuse rather atypical hepatitis for a period of 15 months before the classic picture of sarcoidosis was found at laparotomy.

Branson and Park's [18] patient was a 51-year-old white woman who had involvement of the skin, lungs, liver, spleen, and lymphatics. She complained of fatigue, loss of weight, pruritus, anorexia, and jaundice while under observation for two and one-half years. Objective findings included hepatomegaly, xanthelasma, abnormal cephalin-cholesterol flocculation reactions, increasing icterus indices, increased blood cholesterol, and reversal of the albumin-globulin ratio. Death occurred from intercurrent sepsis. At necropsy, the liver showed increased fibrosis and proliferation of the bile ducts in the portal spaces, along with diffuse sarcoid involvement of a predominantly interlobular distribution.

The last of these six detailed cases of hepatic involvement in sarcoidosis was reported by Kelley and McHardy.[37] The patient was a 48-year-old white man who had protracted jaundice, pruritus, paraumbilical discomfort, and nausea. Hepatosplenomegaly, scleral jaundice, bilirubinuria, anemia, leukopenia, and great increases in the alkaline phosphatase, total cholesterol, and both direct-reacting and indirect-reacting serum bilirubin were the abnormalities recorded. The electrophoretic pattern of the serum showed increased total proteins, with diminution in the albumin, a moderate increase in β-globulin, and a pronounced increase in γ-globulin. Sections of the liver obtained at the beginning of the 12 months of observation showed chronic cholangitis and sarcoid granulomas. His downhill course was not altered by a total dose of 8.2 gm. of cortisone, 900 mg. of corticotropin (ACTH), and a dose of roentgen therapy of 4200r to the liver. Necropsy revealed hepatosplenomegaly and enlarged periaortic and mesenteric nodes. Extensive generalized fibrosis of the hepatic parenchyma with atrophy and compression of many hepatic cords was found. Sarcoids were seen in a mesenteric node but not in the liver or spleen.

CASE 19.—A 24-year-old Negro man was admitted to our hospital in July, 1956, because of fever and jaundice.

From May, 1954, to January, 1955, he had been under constant medical observation elsewhere because of recurring fever, night sweats, epigastric fullness, anorexia, and loss of weight. Leukocytosis, mild anemia, increased sedimentation rate, micropyuria, and minimal albuminuria were found. A thoracic roentgenogram showed a minimal inflammatory process in both lung bases. The usual bacteriologic and immunologic studies for evaluation of fever of unknown origin yielded no positive results. Studies for L. E. cells and sickle cells were negative, as were the skin reactions to histoplasmin, coccidioidin, and tuberculin. The bone marrow was normal. Biopsy of the liver showed parenchymatous degeneration, accumulations of leukocytes about the sinusoids, and increased fibrosis and inflammatory infiltration of the portal spaces. At the end of the period of observation, the febrile episodes had cleared. Results of physical examination had remained normal except for a palpable liver and spleen. He was dismissed with sarcoidosis and Hodgkin's disease considered as likely diagnostic possibilities.

The patient felt well until July, 1956, when a severe hacking cough and exertional dyspnea developed in association with anorexia, loss of weight, chills, fever, scleral jaundice, clay-colored stools, dark urine, and pruritus. There was no history of exposure to hepatotoxins.

On admission to our hospital, his temperature was 100.6 F. The scleras appeared icteric. The liver edge and splenic tip were palpable 2 fingerbreadths below the costal margins. The remainder of the physical examination was normal. Ophthalmologic studies revealed no involvement of the uveal tract.

Pertinent ancillary findings consisted of a sedimentation rate of 37 mm. during the first hour, sterile routine cultures of urine and blood, and negative sputum cultures for tubercle bacilli. The titers of febrile agglutinins, cold agglutinins, agglutinins for leptospirosis, and heterophil antibodies were not diagnostic. Repeated hemograms were normal except for intermittent slight increases in the percentage of eosinophils. Serial thoracic roentgenograms showed increasing mottled and linear densities extending from the hilus into both midlung fields, together with an elevated right hemidiaphragm. Hilar adenopathy was not seen. Roentgenograms of the hands revealed three punched-out radiolucent zones, 1 to 2 mm. in diameter, in the phalanges. A plain roentgenogram

TABLE 5.—*Liver-Function Tests in Case 19*

	July 25	July 30	Aug. 6	Aug. 12	Aug. 20	Sept. 4	Sept. 19	Oct. 3	Oct. 10	Oct. 17	Oct. 30	Nov. 7	Nov. 21	Nov. 28
Total serum bilirubin, mg./100 ml.	4.8	6.2	10.6	12.4	3.2	3.0	1.4	0.86	2.0	1.6	1.6	1.76	2.8	3.4
Direct-reacting serum bilirubin, mg./100 ml.	2.4	3.1	4.4	5.8	1.6	1.6	0.7	0.42	1.2	0.8	0.8	1.33	1.1	1.7
Serum alkaline phosphatase, mod. Bodansky units	77.6	143	92.3	71.4	50	64	68	69	51.3	89.4	73.8	50.5	65.8	51
Serum cholesterol, mg./100 ml.	...	...	570	265	...	600	...	...	...	...	...	430	...	325
Thymol turbidity (normal=6 units)	6	...	4	6.4	10	4	2	5	3	2	4	3.4	5	6
Cephalin-cholesterol flocculation (48 hr.)	1+	...	...	1+	1+	...	2+	Trace	...	2+	Trace	Trace	...	1
Prothrombin time, sec. (control=13 sec.)	14	...	...	...	15	16	...	...	...	...	...	...	...	...
Bilirubinuria	Pos.	...	...	Pos.	...	...	Neg.	...	...	Neg.	...	...	...	...
Urobilinuria	+1:30	...	...	...	...	...	+1:1	...	...	+1:1	...	...	...	...

of the abdomen disclosed enlargement of the liver and spleen. Tuberculin, coccidioidin, and histoplasmin skin tests performed shortly after entry gave negative reactions. Values for serum calcium and inorganic phosphorus were normal. Total serum proteins measured 8.6 gm. per 100 ml., with 4.1 gm. of albumin and 4.5 gm. of globulin. Results of liver-function tests are contained in Table 5. A Kveim test during therapy with cortisone gave no reaction.

The patient's early hospital course was characterized by recurring fever, with temperature to 102 F, and by persistence of anorexia, malaise, and pruritus. The jaundice increased, with a maximal total serum bilirubin of 12.4 mg. on Aug. 12, 1956. Biopsy of a right scalene node was not diagnostic. Biopsy of the liver was deferred because of the pattern of obstructive jaundice. A presumptive diagnosis of sarcoidosis was made in view of the protracted clinical course, with pulmonary, osseous, hepatic, and splenic involvement in the presence of negative studies for tuberculosis. On Aug. 16, oral therapy with cortisone, 50 mg. every six hours, was begun. Isoniazid, 100 mg. three times daily, and aminosalicylic acid, 12 gm. daily, were given concomitantly. Shortly thereafter, the patient showed great objective and subjective improvement, with a sharp decrease in serum bilirubin to 3.2 mg., diminution of pruritus, and disappearance of fever and anorexia. The liver and spleen remained palpable. The dose of cortisone was gradually diminished, and by Sept. 8, he was taking 25 mg. three times daily. On Sept. 12, a febrile episode without localizing findings developed. The dose of cortisone was increased to 25 mg. every six hours; by Sept. 17, he was again afebrile and asymptomatic.

On Sept. 20, biopsy of the liver was done. The hepatic cells appeared well preserved. The portal zones showed moderate lymphocytic infiltration and occasional eosinophils. The ducts appeared essentially normal. Several small well-circumscribed zones consisting of proliferating fibroblasts and lymphocytes, with one giant cell, were seen. The diagnosis was chronic granuloma compatible with Boeck's sarcoid. The dose of cortisone was progressively reduced, and all medication was discontinued on Oct. 7. By Oct. 10, malaise, anorexia, fever, and jaundice reappeared. Five days later, the patient's temperature reached 105 F. Causes for this relapse other than reactivation of sarcoidosis could not be found, and administration of cortisone plus prophylactic antituberculotic drugs again was started, with prompt resolution of signs and symptoms. The oral dose of cortisone was gradually decreased, and a minimum of 37.5 mg. given daily was found necessary to maintain a normal temperature. In November, 1956, this pa-

tient was transferred to the United States for further care.

The evolution of the hepatic changes in this patient, as demonstrated by biopsy on two occasions, is of considerable interest. The first biopsy disclosed only inflammatory infiltration of the portal spaces, while the second, done two years later, showed the additional presence of an epithelioid granuloma. In this respect, our patient resembled the one reported by Wagoner and associates.[40]

The appearance of jaundice was the first distinctive indication of predominant hepatic involvement in our case. The pattern of pruritus, normal results of flocculation tests, and progressive increases in bilirubin, alkaline phosphatase, and serum cholesterol was compatible with extrahepatic obstruction secondary to pressure from enlarged abdominal lymph nodes. An alternative possibility was parenchymal sarcoid involvement producing a derangement in hepatic function similar to that found in some cases of viral hepatitis or in the jaundice complicating administration of chlorpromazine or methyltestosterone. Use of cortisone produced a striking decrease in serum bilirubin without appreciably affecting the values for alkaline phosphatase or cholesterol. This pointed toward parenchymal involvement and obviated an exploratory laparotomy. The intravenous administration of corticotropin as a diagnostic tool in intrahepatic obstructive jaundice has recently been advocated by Johnson and Doenges,[41] who reported two cases of hepatitis in which the technique was used successfully.

The high levels of alkaline phosphatase in the blood of our patient are in keeping with the findings recorded in similar cases of hepatic sarcoidosis and merit special comment in view of the recent report by Ross and co-workers,[42] who found increased serum alkaline phosphatase with essentially normal bilirubin in patients with a variety of infiltrative hepatic diseases.

The electrophoretic pattern of our patient's plasma proteins was determined on three occasions, and it showed a persistent decrease in albumin and α_1-globulin, with substantial increases in γ-globulin. Similar findings have been described by others in sarcoidosis and also in severe hepatitis and portal cirrhosis with ascites.

Mucous Membranes.—Involvement of the mucous membranes by sarcoidosis occurs with much less frequency than does involvement of the lymph nodes, lungs, liver, spleen, or bones. When it occurs, it is said to be attended always by involvement of the other organ systems, particularly the lymphatics. Involvement of the nasal mucosa was present in one of Boeck's original cases. Kistner and Robertson[43] reported a case in which sarcoidosis apparently affected only the nasal mucous membranes, the nasal bones, and the skin of the nose. Of the 35 patients studied by Reisner,[3] 4 had sarcoidosis of mucous membranes. Rubin and Kling[44] reviewed the reported cases of intranasal sarcoidosis and added one case of their own with involvement of the nasal septum and eventually of the nasal bones and overlying skin. Robinson and Pound,[45] in a review of 30 cases of sarcoidosis, noted histologic evidence of lesions of the nasal mucosa in 6 cases and atrophic rhinitis in 3. Atrophic rhinitis as a complication of sarcoidosis also was found in three cases at the Massachusetts General Hospital.[5]

According to Longcope and Freiman,[5] involvement of the oral mucosa is rare, but epithelioid bodies are found sometimes in the pharynx, larynx, and epiglottis. Spencer and Warren[46] reported a case of widespread sarcoidosis with terminal laryngeal edema and necropsy confirmation of tracheal involvement. Endobronchial granulomas in systemic sarcoidosis, even in the absence of gross changes, occur not infrequently, as shown by the high incidence of positive results of biopsy done during routine bronchoscopic examination in patients with sarcoidosis.

Our Case 5 was of particular interest because of nasal obstruction and laryngeal involvement that responded to treatment with adrenal cortical steroids.

CASE 5.—A 28-year-old Negro woman was first admitted to our hospital in March, 1955, because of nasal obstruction. Her illness probably commenced in the latter part of 1950, when she noted enlarged epitrochlear lymph nodes. In May, 1951, bilateral hilar adenopathy was found in a routine thoracic roentgenogram. She was asymptomatic at that time, but examination disclosed nodular lesions in her ear lobes and eyelids, generalized adenopathy, and hypertrophy of the nasal mucous membranes. Results of a tuberculin test were negative. Biopsy of a left cervical node performed elsewhere was compatible with the diagnosis of sarcoidosis. In October, 1951, she began to have recurring episodes of sneezing with nasal obstruction, and biopsy of the nasal mucosa showed sarcoid granulomas. In the spring of 1952, submucous resection and partial excision of the granulomatous tissues in the nose were performed, with only temporary improvement. She was then treated orally with 100 mg. of cortisone per day for three months, with great improvement. The medication was discontinued because of the appearance of edema and albuminuria. Improvement persisted until the summer of 1953, at which time nasal obstruction and peripheral adenopathy began to recur. By 1955, virtually complete obliteration of the nasal passages had occurred, resulting in her admission to our hospital.

Examination showed generalized lymphadenopathy and nodular lesions about the ear lobes, eyelids, and lips. Inflammatory involvement of the nasal mucosa was apparent, and a granulomatous mass occluded the left nostril. Roentgenograms of the hands showed small cystic zones in the carpal bones of both wrists and in the head of the right first metacarpal. A hemogram was normal; the sedimentation rate was 37 mm. Thymol turbidity, cephalin-cholesterol flocculation, blood urea nitrogen, total proteins, the albumin-globulin ratio, and serum calcium were normal. Biopsy of the lesion in the lateral wall of the left nostril revealed noncaseating granulomas compatible with sarcoidosis. Some improvement followed this procedure, and the patient was dismissed with the advice to take local vasoconstrictors.

In June, 1955, she was again admitted with recurrent nasal obstruction. The physical findings were unchanged. Results of additional laboratory studies were normal except for minimal eosinophilia, a sedimentation rate of 45 mm., and a serum globulin value of 3.05 gm. Roentgenograms of the thorax were unchanged, and those of the paranasal sinuses showed thickening of the membranes of the frontal, ethmoid, and left maxillary sinuses. A tuberculin test gave no reaction. Biopsy of a lesion on the lip showed chronic inflammation without the epithelioid tubercles of sarcoidosis. On July 8, she was given cortisone in oral doses of 50 mg. every six hours, with prompt improvement in her obstructive symptoms. By July 12, the otolaryngologist was able to see all of her nasal passages for the first time, the granulomatous region in the left nostril having entirely resolved. Improvement was sustained. By July 15, the peripheral adenopathy appeared somewhat diminished, without any change in the hilar involvement. The lip lesions had become barely perceptible. The dose of cortisone was reduced to 25 mg. every six hours, and she was dismissed from the hospital on July 22. Use of cortisone was discontinued in November, 1955, because of nausea, vomiting, recurring furunculosis, and the development of an indolent vaginal discharge. The clinical remission in her obstructive nasal symptoms persisted on a program of increased rest in bed, but the lip lesions and peripheral nodes returned to the precortisone state.

In September, 1956, she returned because of increasing hoarseness, anosmia, and nasal obstruction. The nose was almost obliterated by granular-appearing lesions, although nasal breathing was still possible. Granular lesions were also seen about the epiglottis and the larynx overlying, but not involving, the cords. Results of a Kveim test were positive clinically.

In November, 1956, tuberculin, coccidioidin, and histoplasmin skin tests gave no reactions. The patient was then given Δ-*1*-hydrocortisone, 5 mg. every eight hours, together with 1 gm. of potassium chloride and 100 mg. of isoniazid. She again experienced great objective and subjective improvement within a few days of the commencement of treatment. The positive Kveim papule disappeared within two weeks. The dose of Δ-*1*-hydrocortisone was diminished to 10 mg. daily because of the advent of insomnia and euphoria. Hoarseness disappeared, and the nasal passages remained patent, but anosmia persisted and the lip lesions appeared to be regressing to pretreatment size. Thoracic roentgenograms remained unchanged. She was last seen in February, 1957. Her improvement appeared sustained on the above regimen, without side-effects from therapy.

Retina.—Retinal sarcoidosis is apparently an extremely rare manifestation of ocular sarcoidosis. Only eight cases of granulomatous retinal lesions have been reported to our knowledge.[47-54] Walsh [49] described yellow-white nodules in the fundus that tended toward a perivascular distribution with associated retinal periphlebitis. He speculated the relationship of the lesions to the retinal vessels might be characteristic of intraocular sarcoid. Levitt [50] reported a case of severe

ocular sarcoidosis involving the anterior uveal tract as well as the retina and choroid. Microscopic examination revealed extensive retinal periphlebitis, endophlebitis, and arteritis characterized by mantling of the vessels with lymphocytes and proliferative changes leading to occlusion of the lumen and, in many instances, to complete replacement of the vessel wall by epithelioid cells. Larger nodules that did not appear to originate from vessel walls also were found. MacDonald [51-52] presented histologic sections of similar nodules that revealed the typical structure of sarcoid granulomas. These granulomas have been known to bulge into the vitreous or at times to penetrate into the choroid.[54]

Hemorrhagic retinitis has been found in rare instances of sarcoidosis. Two such cases occurred in The Johns Hopkins series,[5] and Dressler and Wagner [55] described a similar situation associated with periphlebitis. Optic neuritis and optic atrophy also have been reported as complications of sarcoidosis.

Retinal lesions are to be distinguished from the even rarer choroidal nodules. These are described as yellowish nodules without apparent involvement of the overlying retina. With healing, discrete zones of chorioretinitis may be seen as a residual.

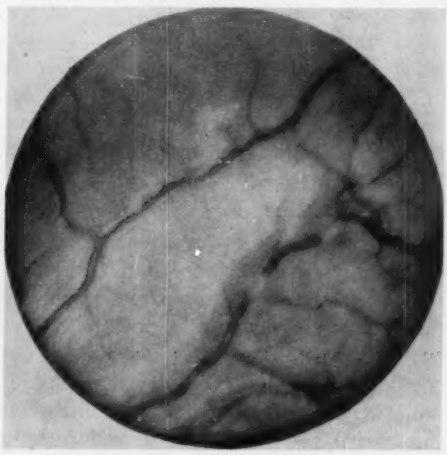
One of our patients exhibited asymptomatic involvement of the ocular fundus.

CASE 22.—An 18-year-old Negro boy was admitted to the hospital in September, 1956, for evaluation of "swollen glands" in the neck first noticed four days prior to entry. Examination revealed pronounced generalized lymphadenopathy, with especially prominent epitrochlear and femoral nodes. An ophthalmologic consultant reported no evidence of ocular changes. Leukocytes numbered 4600, with a normal differential count. The sedimentation rate was 12 mm. Results of other laboratory studies, including hemoglobin, flocculation test for syphilis, heterophil antibody titer, L. E.-cell preparation, urinalysis, and serum calcium, phosphorus, total proteins, and albumin-globulin ratio were within normal limits. Tuberculin, coccidiodin, and histoplasmin skin tests gave no reactions. Thoracic roentgenograms showed massive hilar adenopathy and hazy infiltration in both lung fields. Roentgenograms of the hand revealed zones of punctate radiolucency interpreted as compatible with sarcoidosis. Biopsy of a left cervical node disclosed typical sarcoid epithelioid granulomas. Culture of this tissue gave no growth of tubercle bacilli or fungi. A Kveim test produced a papule that was positive on biopsy after six weeks. Serial thoracic roentgenograms revealed no change in the hilar adenopathy, but complete resolution of the parenchymal infiltration was noted by November. During this period, the patient had no complaints except for discomfort in the inguinal region on prolonged walking attributed to the massive lymphadenopathy.

In December, 1956, he was again referred to Dr. Jorge Buxton for ophthalmologic evaluation. Discrete gray keratic precipitates were noted bilaterally, more pronounced on the right cornea. No other changes in the uveal tract were found. The fundus contained small yellowish-white nodules adjacent to or overriding several retinal veins bilaterally. Perivenous streaking was noted in some regions, and its distribution was not consistently related to the nodules. Figures 1 and 2 are retinal photographs demonstrating these findings. These lesions were thought to represent sarcoid nodules with accompanying periphlebitis. In places there was a suggestion that the venous lumen was narrowed by the nodules. Extension into the vitreous was not seen, and choroidal involvement was not evident. The patient at that time had no ocular symptoms whatever.

By Feb. 5, 1957, only phantom remnants of the retinal nodules persisted and all evidence of periphlebitis had vanished. No alteration of the caliber of the veins could be seen at the sites of

Fig. 1 (Case 22).—Retinal photograph in sarcoidosis. Two nodules are present on the inferior blood vessel. Perivenous streaking is seen along the superior vein.



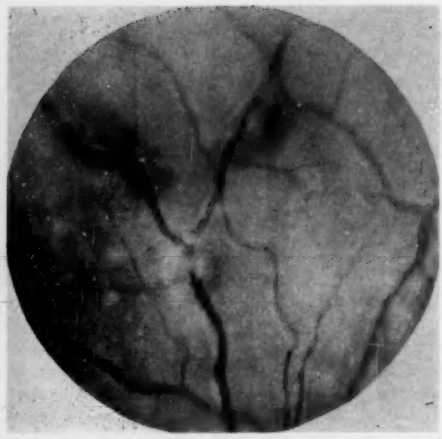


Fig. 2 (Case 22).—Retinal photograph in sarcoidosis. Two nodules are present near the venous bifurcation. Extensive periphlebitis is also seen. The white patches to the left of the vein represent high-light artifacts.

the old lesions. The keratic precipitates on the right cornea had increased, but involvement on the left was unchanged. No anterior-chamber flare was seen. On Feb. 13, left iridocyclitis appeared and required topical treatment with cortisone. Within a week the process became quiescent. The patient has continued under observation; new retinal lesions have not appeared.

Joints.—Arthritic manifestations in sarcoidosis have not been widely noted and pathologic material documenting synovial involvement has been particularly scanty. Burman and Mayer [56] reported extensive studies of an 8-year-old girl who had involvement of the elbow and knee joints plus boggy masses in the tendon sheaths of the ankles and wrists of three years' duration. There was no redness, heat, or tenderness in the affected regions. Synovectomy revealed grape-like clusters of sarcoid tissue arising from the synovium, as well as a "pannus" of sarcoid granulations on the tendons and femoral condyles.

Most cases of joint involvement reported in recent years have been characterized by febrile polyarthritis resembling rheumatic fever except for its refractoriness to salicylate therapy.[8,15,57] Erythema nodosum has been associated in a high percentage of instances, and resolution without residual joint damage has been the rule. James [58] recently reported that 34 of 150 patients with sarcoidosis had erythema nodosum with or without arthritis when first seen. Myers and associates [59] found that biopsy of random muscles revealed sarcoid granulomas in three of their four arthritic patients. Results of synovial biopsy have not been reported heretofore in this syndrome to our knowledge.

A third type of articular involvement seen in sarcoidosis is secondary to extensive bony lesions in the hands. Juxta-articular demineralization, marginal erosion, and subluxation may occur. The roentgenographic appearance in the case of Moyer and Ackerman [12] resembled that of rheumatoid arthritis, but clinically there was no inflammatory reaction in the overlying soft tissue during the evolution of the lesions. Rarely, the mechanical displacement has resulted in mutilating deformities and occasionally has required amputation of phalanges.

One of our patients had febrile polyarthritis that responded incompletely to salicylate therapy.

Case 29.—A 23-year-old Negro man was transferred to this hospital in May, 1957. Late in March a mild cough developed that was productive of mucoid sputum. Early in April, he began to experience aching and stiffness of his elbows, wrists, knees, and ankles. This was maximal on arising and tended to diminish as the day progressed. On admission to his local hospital on April 10, 1957, a swollen right wrist and tender ankles were apparent. A daily increase of temperature to 101 F was recorded. A roentgenogram of the thorax revealed bilateral hilar adenopathy, with patchy parenchymal miliary infiltrates in the left midlung field and right base. Laboratory work revealed leukocytosis, accelerated sedimentation rate, and increased serum globulin. Medication with large doses of salicylates diminished the fever and eliminated the subjective joint complaints for a period of three weeks prior to transfer.

On admission to our hospital, both wrists and both ankles exhibited slight swelling, increased warmth, and some limitation of range. Palpable effusion was present in the knees, and there were bilateral tenderness and swelling about the fourth metatarsophalangeal joint. Despite the objective changes, the patient experienced little discomfort at rest or with use of the joints. No other notable physical findings were present aside from continued intermittent increase of temperature to 101 F

each afternoon. Abnormal laboratory findings included a sedimentation rate of 34 mm. during the first hour, serum globulin of 3.3 gm. per 100 ml., and C-reactive protein of 2+. The antistreptolysin titer was between 12 and 50 Todd units. Tuberculin, coccidioidin, and histoplasmin skin tests yielded negative reactions. Routine blood cell counts, urinalysis, flocculation reaction for syphilis, blood calcium, and total serum proteins were not remarkable. L. E.-cell preparations were not diagnostic on several occasions. Routine blood cultures and cultures of gastric contents for tubercle bacilli had been found negative prior to transfer. Serial electrocardiograms during the course of the patient's illness revealed no abnormal changes. Roentgenograms of the peripheral joints remained normal, and those of the thorax showed unchanged hilar adenopathy and pulmonary infiltrates.

Joint fluid from the right knee contained 2575 leukocytes per cubic millimeter, with 93% lymphocytes. Clotting did not occur, and the value for total protein was 4.1 gm. per 100 ml. The acetic acid test for mucin yielded a flocculent precipitate in a cloudy solution. The fluid was sterile.

Synovial biopsy of the right knee revealed mild infiltration of mononuclear inflammatory cells around small blood vessels and into the synovial layer itself. Biopsy of the right gastrocnemius muscle was not diagnostic. Dissection of the right scalene nodes yielded tissue that contained typical sarcoid granulomas. Results of a Kveim test were positive grossly and histologically.

A trial of therapy with acetylsalicylic acid, 6.6 gm. daily in divided doses, was conducted. The daily fever was decreased by 1 F, but there was no remarkable effect on the joint manifestations or laboratory abnormalities. Hydrocortisone was injected into the right knee joint in doses of 50 mg. on two occasions, but the response was not impressive. Over the course of four weeks, the arthritis gradually disappeared, and no residual changes were detectable.

Because of persistent fever and extensive pulmonary involvement, this patient was transferred to the United States for further care in July, 1957.

Treatment

It is difficult to assess the value of any regimen in the management of an illness characterized by a relatively benign, protracted, and fluctuating course. Roentgen rays, calciferol, and antituberculotic drugs appear to have no beneficial effects in sarcoidosis. Prolonged rest in bed has been advocated during the active stages of the disease. Administration of corticotropin and cortisone has been considered capable of modifying the proliferative stages of sarcoidosis. The acceleration of healing apparently produced by steroids may not always be of benefit to the patient, for fibrosis of the affected organs with subsequent impairment of function theoretically may result. This was illustrated in the seven patients with involvement of the lungs whose pulmonary function was studied before and after steroid therapy by Stone and associates.[60] Three of these patients had complete or partial restoration of function, while four actually showed deterioration during the period of therapy. James[58] found hyalinization of lesions in the nose and in Kveim papules after one to three months of steroid therapy. Israel and coworkers[61] reported their experience with 36 patients with sarcoidosis, manifested predominantly by ocular involvement and progressive respiratory disease, who were given cortisone for several months. Clinical improvement from slight to dramatic resulted in 34 of the 36 symptomatic patients during treatment; the changes were more pronounced in those whose illness was of short duration. However, only 55% of the patients showed evidence of improvement at the end of the period of observation, while 46% of a comparable group of untreated patients were better.

A possible danger of steroid therapy is the activation of tuberculosis. This occurred in 4 of the 10 patients with sarcoidosis treated with cortisone by Lovelock and Stone.[62] These patients had negative reactions to tuberculin prior to the administration of cortisone, but they converted to a state of sensitivity shortly after the initiation of therapy. Bacteriologic proof of active tuberculosis was then found. Contrary to this experience is the absence of tuberculous activation in the 36 patients treated with cortisone by Israel's[61] group.

Certain components of the over-all picture of sarcoidosis appear to be more susceptible to administration of steroids than do others.

This applies to uveitis, fever, and parotitis, as well as to the renal complications associated with hypercalcemia. James [58] mentioned disfiguring cutaneous lesions, neurologic involvement, and progressive pulmonary disease as additional indications for steroid therapy.

Our experiences allowed us to draw only limited conclusions concerning the treatment of sarcoidosis. The patients who exhibited pronounced roentgenologic evidence of pulmonary involvement had no symptoms necessitating any therapy. The magnitude of tracheal or hilar adenopathy was never such as to produce obstructive manifestations in any of our patients. We limited the use of steroids to those patients for whom such treatment appeared compulsory in view of the clinical picture. In Case 13, cortisone was used because of hypersplenism with panhematopenia; treatment effected a remarkable decrease in splenic size and a concomitant surge in hematopoiesis. Other observers also have noted a decrease in splenic size with adrenal cortical therapy. Meningitis developed during treatment in this case. The absence of definitive bacteriologic findings in the presence of a decreased cerebrospinal fluid sugar made it imperative to regard the meningitis as tuberculous in origin. Accordingly, antituberculotic drugs were administered to this patient and later were given prophylactically to our other patients with sarcoidosis who received adrenal steroids. Cortisone was given in Case 19 because of the increasing serum bilirubin and alkaline phosphatase in an effort to differentiate between intrahepatic and extrahepatic obstruction. Treatment not only averted laparotomy but resulted in much objective and subjective improvement. In Case 5, steroids were given because of the extreme discomfort produced by the nasal obstruction and the fear of progression of laryngeal involvement. This patient tolerated Δ-1-hydrocortisone better than she did cortisone, although improvement was obtained with both hormones.

Summary and Conclusions

A study was made of 29 patients proved to have sarcoidosis and seen on the medical service of the 7100th U. S. A. F. Hospital in a 29-month period.

The unusually high incidence rate encountered in this study may reflect partially the inclusion of a number of asymptomatic patients and suggests that the disease is more prevalent than is commonly recognized. A predilection for sarcoidosis apparently exists in both white and Negro patients who have lived in the southeastern part of the United States. The incidence rate for Negroes in this series was 12 times that of white persons.

Five unusual cases with splenic, hepatic, mucous-membrane, retinal, and joint manifestations are described in detail, with a brief review of the pertinent literature regarding these features.

The use of adrenal steroids in the management of certain complications of sarcoidosis is discussed.

Section of Medicine, Mayo Clinic, Rochester, Minn. (Capt. Paris).

REFERENCES

1. Hutchinson, J.: Illustrations of Clinical Surgery Consisting of Plates, Photographs, Woodcuts, Diagrams, Etc. Illustrating Surgical Diseases, Symptoms and Accidents: Also, Operative and Other Methods of Treatment, with Descriptive Letter-Press, London, J. & A. Churchill, Ltd., 1875, Folio, p. 42.

2. Pinner, M.: Noncaseating Tuberculosis: An Analysis of the Literature, Am. Rev. Tuberc. 37: 690-728 (June) 1938.

3. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): A Study of 35 Cases, Am. Rev. Tuberc. 49:289-307 (April) 1944.

4. Ricker, W., and Clark, M.: Sarcoidosis: A Clinicopathologic Review of 300 Cases, Including 22 Autopsies, Am. J. Clin. Path. 19:725-749 (Aug.) 1949.

5. Longcope, W. T., and Freiman, D. G.: Study of Sarcoidosis Based on Combined Investigation of 160 Cases Including 30 Autopsies from Johns Hopkins Hospital and Massachusetts General Hospital, Medicine 31:1-132 (Feb.) 1952.

6. Michael, M., Jr.; Cole, R. M.; Beeson, P. B., and Olson, B. J.: Sarcoidosis: Preliminary Report

on Study of 350 Cases with Special Reference to Epidemiology, Am. Rev. Tuberc. 62:403-407 (Oct.) 1950.

7. Schönholzer, G.: Morbus Besnier-Boeck-Schaumann und Armeedurchleuchtung, Schweiz. med. Wchnschr. 77:585-588 (May 31) 1947.

8. Riley, E. A.: Boeck's Sarcoid: Review Based upon Clinical Study of 52 Cases, Am. Rev. Tuberc. 62:231-285 (Sept.) 1950.

9. Carr, D. T., and Gage, R. P.: The Geographic Distribution of Sarcoidosis, Am. Rev. Tuberc. 70: 899-900 (Nov.) 1954.

10. Cummings, M. M.; Dunner, E.; Schmidt, R. H., Jr., and Barnwell, J. B.: Concepts of Epidemiology of Sarcoidosis: Preliminary Report of 1194 Cases Reviewed with Special Reference to Geographic Ecology, Postgrad. Med. 19:437-446 (May) 1956.

11. McCort, J. J.; Wood, R. H.; Hamilton, J. B., and Ehrlich, D. E.: Sarcoidosis: A Clinical and Roentgenologic Study of 28 Proved Cases, Arch. Int. Med. 80:293-321 (Sept.) 1947.

12. Moyer, J. H., and Ackerman, A. J.: Sarcoidosis: A Clinical and Roentgenological Study of 28 Cases, Am. Rev. Tuberc. 61:299-322 (March) 1950.

13. Sones, M., and Israel, H. L.: Altered Immunologic Reactions in Sarcoidosis, Ann. Int. Med. 40:260-268 (Feb.) 1954.

14. Israel, H. L., and Sones, M.: The Diagnosis of Sarcoidosis with Special Reference to the Kveim Reaction, Ann. Int. Med. 43:1269-1282 (Dec.) 1955.

15. Siltzbach, L. E., and Ehrlich, J. C.: The Nickerson-Kveim Reaction in Sarcoidosis, Am. J. Med. 16:790-803 (June) 1954.

16. Rogers, F. J., and Haserick, J. R.: Sarcoidosis and the Kveim Reaction, J. Invest. Dermat. 23:389-406 (Nov.) 1954.

17. Hodgson, C. H., and Woolner, L. B.: Symposium on Bronchial and Pulmonary Diseases: Diagnosis and Treatment of Pulmonary Sarcoidosis, M. Clin. North America 38:997-1008 (July) 1954.

18. Branson, J. H., and Park, J. H.: Sarcoidosis—Hepatic Involvement: Presentation of a Case with Fatal Liver Involvement, Including Autopsy Findings and Review of the Evidence for Sarcoid Involvement of the Liver as Found in the Literature, Ann. Int. Med. 40:111-145 (Jan.) 1954.

19. Crane, A. R., and Zetlin, A. M.: Hemolytic Anemia, Hyperglobulinemia, and Boeck's Sarcoid, Ann. Int. Med. 23:882-889 (Nov.) 1945.

20. Bruschi, M., and Howe, J. S.: Classification of the Hematologic Variations and Abnormalities Associated with Boeck's Sarcoid: Review of the Literature; Report of Case of Thrombocytopenic Purpura Associated with Sarcoidosis, with Recovery Following Splenectomy, Blood 5:478-490 (May) 1950.

21. Stats, D.; Rosenthal, N., and Wasserman, L. R.: Hemolytic Anemia Associated with Malignant Diseases, Am. J. Clin. Path. 17:585-613 (Aug.) 1947.

22. Jersild, M.: The Syndrome of Heerfordt (Uveo-Parotid Fever), a Manifestation of Boeck's Sarcoid, Acta. med. scandinav. 97:322-328, 1938.

23. Berblinger, W.: Zur Kenntnis der atypischen Tuberkulose (Morbus Boeck?), Acta davosiana 5:1, 1939.

24. Kraus, E. J.: Sarcoidosis (Boeck-Besnier-Schaumann Disease) as Cause of Pituitary Syndrome, J. Lab. & Clin. Med. 28 (Pt. 1):140-146 (Nov.) 1942.

25. Enzer, N.: Generalized Boeck's Sarcoidosis with Thrombocytopenic Purpura, Abstract, Am. J. Path. 22:663-664 (June) 1946.

26. Nordland, M.; Ylvisaker, R. S.; Larson, P., and Reiff, R.: Pregnancy Complicated by Idiopathic Thrombocytopenic Purpura and Sarcoid Disease of the Spleen; Splenectomy and Subsequent Normal Delivery: Case Report, Minnesota Med. 29:166-170 (Feb.) 1946.

27. Freiman, D. G.: Medical Progress: Sarcoidosis, New England J. Med. 239:664-671 (Oct. 28) 1948.

28. Dameshek, W., and Estren, S.: The Spleen and Hypersplenism, A Reprint of an Exhibit Presented at the 100th Anniversary Convention of the American Medical Association, Atlantic City, June, 1947, New York, Grune & Stratton, Inc., 1947.

29. Kunkel, P., and Yesner, R.: Thrombocytopenic Purpura Associated with Sarcoid Granulomas of the Spleen, Arch. Path. 50:778-786 (Dec.) 1950.

30. Wright, C. S.; Doan, C. A.; Bouroncle, B. A., and Zollinger, R. M.: Direct Splenic Arterial and Venous Blood Studies in the Hypersplenic Syndromes Before and After Epinephrine, Blood 6:195-212 (March) 1951.

31. Ehrlich, L., and Schwartz, S. O.: Splenomegaly in Thrombocytopenic Purpura, Am. J. M. Sc. 221:158-168 (Feb.) 1951.

32. Cattell, R. B., and Wilson, R. O.: Sarcoidosis of the Spleen: Report of 2 Cases, Lahey Clin. Bull. 7:66-71 (Jan.) 1951.

33. Edwards, M. H.; Wagner, J. A., and Krause, L. A. M.: Sarcoidosis with Thrombocytopenia: Report of a Case, Ann. Int. Med. 37:803-812 (Oct.) 1952.

34. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura, a Form of Hypersplenism, Blood 1:27-51 (Jan.) 1946.

35. Schrijver, H., and Schillings, P. H. M.: Thrombocytopenic Purpura with Sarcoidosis,

Cured After Splenectomy, Acta med. scandinav. 144:213-216, 1952.

36. Shay, H.; Berk, J. E.; Sones, M.; Aegerter, E. E.; Weston, J. K., and Adams, A. B.: The Liver in Sarcoidosis Gastroenterology 19:441-461 (Nov.) 1951.

37. Kelley, M. L., Jr., and McHardy, R. J.: An Unusual Case of Fatal Hepatic Sarcoidosis, Am. J. Med. 18:842-850 (May) 1955.

38. Klatskin, G., and Yesner, R.: Hepatic Manifestations of Sarcoidosis and Other Granulomatous Diseases: A Study Based on Histological Examination of Tissue Obtained by Needle Biopsy of the Liver, Yale J. Biol. & Med. 23:207-248 (Dec.) 1950.

39. Mino, R. A.; Frelick, R. W.; Murphy, A. I., Jr., and Hooker, J. W.: Severe Systemic Sarcoidosis with Ascites and Splenomegaly, Delaware M. J. 20:65-75 (April) 1948.

40. Wagoner, G. P.; Freiman, D. G., and Schiff, L.: An Unusual Case of Jaundice in a Patient with Sarcoidosis, Gastroenterology 25:574-581 (Dec.) 1953.

41. Johnson, H. C., Jr., and Doenges, J. P.: Intrahepatic Obstructive Jaundice (Primary Cholestasis), a Clinicopathologic Syndrome of Varied Etiology: A Review with Observations of the Use of Corticotropin as a Diagnostic Tool, Ann. Int. Med. 44:589-616 (April) 1956.

42. Ross, R. S.; Iber, F, L., and Harvey, A. M.: The Serum Alkaline Phosphatase in Chronic Infiltrative Disease of the Liver, Am. J. Med. 21:850-856 (Dec.) 1956.

43. Kistner, F. B., and Robertson, T. D.: Benign Granuloma of the Nose (So-Called Sarcoid), J. A. M. A. 111:2003-2005 (Nov. 26) 1938.

44. Rubin, H. J., and Kling, D. H.: Boeck's Sarcoid of the Nasal Vault, Ann. Otol. Rhin. & Laryng. 57:1083-1087 (Dec.) 1948.

45. Robinson, B., and Pound, A. W.: Sarcoidosis: A Survey, with Report of 30 Cases, M. J. Australia 2:568-582 (Oct. 14) 1950.

46. Spencer, J., and Warren, S.: Boeck's Sarcoid: Report of a Case, with Clinical Diagnosis Confirmed at Autopsy, Arch. Int. Med. 62:285-296 (Aug.) 1938.

47. Hudelo, and Rabut: Lupoïdes disséminées de Bœck, Bull. Soc. franç. dermat. et syph. 32:108-109 (March 12) 1925.

48. King, M. J.: Ocular Lesions of Boeck's Sarcoid, Tr. Am. Ophth. Soc. 37:422-458, 1939.

49. Walsh, F. B.: Ocular Importance of Sarcoid: Its Relation to Uveoparotid Fever, Arch. Ophth. 21:421-438 (March) 1939.

50. Levitt, J. M.: Boeck's Sarcoid with Ocular Localization: Survey of the Literature and Report of a Case, Arch. Ophth. 26:358-388 (Sept.) 1941; Correction 26:715 (Oct.) 1941.

51. MacDonald, A. E.: So-Called Primary Retinal Tuberculosis, Tr. Am. Ophth. Soc. 41:197-199, 1943.

52. MacDonald, A. E.: Boeck's Sarcoid of Retina—Miliary Form, Tr. Am. Ophth. Soc. 41: 200-204, 1943.

53. Goldberg, S., and Newell, F. W.: Sarcoidosis with Retinal Involvement: Report of 2 Cases, Arch. Ophth. 32:93-96 (Aug.) 1944.

54. Woods, A. C.: Sarcoidosis: The Systemic and Ocular Manifestations, Tr. Am. Acad. Ophth. 53:333-343 (March-April) 1949.

55. Dressler, M., and Wagner, H.: Über zwei Fälle von Lymphogranulomatosis benigna (Schaumann), Acta dermat-venereol. 22:511-542 (Dec.) 1941.

56. Burman, M. S., and Mayer, L.: Arthroscopic Examination of the Knee Joint: Report of Cases Observed in the Course of Arthroscopic Examination, Including Instances of Sarcoid and Multiple Polypoid Fibromatosis, Arch. Surg. 32:846-874 (May) 1936.

57. Gendel, B. R.; Young, J. M., and Greiner, D. J.: Sarcoidosis: A Review with 24 Additional Cases, Am. J. Med. 12:205-218 (Feb.) 1952.

58. James, D. G.: Diagnosis and Treatment of Sarcoidosis, Brit. M. J. 2:900-904 (Oct. 20) 1956.

59. Myers, G. B.; Gottlieb, A. M.; Mattman, P. E.; Eckley, G. M., and Chason, J. L.: Joint and Skeletal Muscle Manifestations in Sarcoidosis, Am. J. Med. 12:161-169 (Feb.) 1952.

60. Stone, D. J.; Schwartz, A.; Feltman, J. A., and Lovelock, F. J.: Pulmonary Function in Sarcoidosis: Results with Cortisone Therapy, Am. J. Med. 15:468-476 (Oct.) 1953.

61. Israel, H. L.; Sones, M., and Harrell, D.: Cortisone Treatment of Sarcoidosis: Experience with 36 Cases, J. A. M. A. 156:461-466 (Oct. 2) 1954.

62. Lovelock, F. J., and Stone, D. J.: The Therapy of Sarcoidosis, Am. J. Med. 15:477-483 (Oct.) 1953.

Chlorpromazine Jaundice

Clinical Course, Hepatic-Function Tests, and Pathologic Findings—Summary of Twenty Cases

WILLIAM F. GEBHART, M.D.; RAY A. VAN OMMEN, M.D.; LAWRENCE J. McCORMACK, M.D., and CHARLES H. BROWN, M.D., Cleveland

Jaundice due to chlorpromazine (Thorazine) hydrochloride has been reported in more than 120 cases in the medical literature. Since our original report of 3 cases,[1] we have seen 17 additional patients with this complication. Several of these patients had prolonged jaundice, and two incurred jaundice during pregnancy.

The clinical and laboratory manifestations of this disease are now well known. It is the purpose of this paper to describe our clinical experience with a comparatively large number of patients having chlorpromazine jaundice and to report in detail findings on liver biopsies that were performed in 15 of our 20 patients.

Incidence and Mechanism

The incidence of jaundice in patients treated with chlorpromazine has been reported to be as low as 0.2%[2,3] and as high as 5%,[4,5] although generally it is considered to approach more nearly 1%.[6] The liver disease so produced usually is regarded as a benign and self-limited condition that can be relieved merely by withdrawal of the drug. However, in some instances the duration of jaundice and of abnormal results of liver-function studies may be protracted.[1,5] In the course of the disease, there also may develop extreme changes in lipid metabolism, which in turn may produce hepatohypercholesteremic cirrhosis[7,8] or primary biliary cirrhosis.[9] In addition, fatalities have been reported in patients having this type of drug-induced liver disease,[10,11] although the conditions of these patients were complicated by some systemic disease.

The mechanism by which chlorpromazine produces a rather specific type of liver disease is not clearly understood. Histologically the changes produced in the liver resemble those caused by arsphenamine, thiouracil, methyltestosterone, and substances of similar chemical structure,[12] the major feature being an intrahepatic obstruction to the flow of bile. Menguy, Bollman, Grindlay, and Cain[13] demonstrated a definite increase in biliary pressure, an increase in biliary sphincter tone, and a decrease in duodenal motility in experimental animals given large doses of chlorpromazine intravenously. These changes were noted to be greater in the fasting animal and in the cholecystectomized animal. It is questionable, however, whether these findings have any clinical significance, since on the basis of body weight the dosages used in the experimental animals would never be used in man. Thus, it is unlikely that an increase in biliary pressure per se plays a significant role in the causative mechanism of this form of liver disease.

Against the theory that ampullar or sphinchter spasm may play an etiologic role is the fact that patients with chlorpromazine jaundice who have undergone operation (including six of our patients) showed no

Submitted for publication Oct. 11, 1957.

This paper is based on a thesis that was submitted by Dr. Gebhart in partial fulfillment of his fellowship requirements at the Cleveland Clinic.

From the Departments of Gastroenterology (Dr. Gebhart, Former Fellow; Dr. Brown, Member of Staff), Internal Medicine (Dr. Van Ommen), and Pathology (Dr. McCormack) of the Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute.

evidence of such spasm or dilatation of the common duct. Several of our patients had operative cholangiograms which also showed no evidence of any sphincter spasm. In a patient having chlorpromazine jaundice, reported to us by another physician, prolonged common duct drainage through a T-tube for more than six months had no beneficial effect on the jaundice, and the patient subsequently died. While all the clinical and laboratory findings indicate that chlorpromazine jaundice is obstructive in nature, such obstruction is not in the sphincter but is in the liver itself.

The likeliest explanation for the production of chlorpromazine jaundice would seem to be an allergic mechanism which leads to intrahepatic cholestasis and bile-plugging. Supporting this concept is the fact that uniformly there appears to be a latent period between the institution of therapy and the development of clinical jaundice or changes in results of hepatic-function tests or both. Further, this reaction reportedly is accelerated in some of those patients who have fully recovered from the disease and who later, by either intention or error, resume treatment with the drug.[14-16] In each of the patients who have had such accelerated reactions it is apparent that the amount of chlorpromazine required to produce the reaction was extremely small. Also, the not infrequent occurrence of a peripheral eosinophilia and of the periportal eosinophilic infiltrate noted on liver biopsy, particularly on biopsy specimens obtained early in the course of the disease,[17] favors the possibility of an allergic mechanism. In opposition to the allergic concept have been reports of cases in which chlorpromazine therapy was reinstituted after complete recovery from the disease without apparent untoward effect [18-20] and the inconsistent results with steroid therapy.[1,12,21]

Shay and Siplet,[16] in careful studies on 47 patients given chlorpromazine, found the serum alkaline phosphatase determination to be the most sensitive means of detecting early sensitivity reactions to chlorpromazine.

Analysis of Cases

Since July 1954, twenty cases of chlorpromazine-induced disease of the liver have been studied at the Cleveland Clinic. Although this condition was diagnosed in six other patients, they have been excluded from this report because of incompleteness of study or lack of follow-up. Of the 20 cases, findings on needle or operative biopsy of the liver are reported for 15; in 4 of these patients, biopsy specimens were obtained on two separate occasions.

All of the patients studied had histories of chlorpromazine ingestion. The total daily dose ranged from 30 to 150 mg., 17 of the patients having received 75 mg. or less. The duration of administration of the drug ranged from 2 to 58 days; eight patients having received the drug for less than 20 days, nine having received it for 20 to 30 days, and three having received it for 42, 49, and 58 days, respectively. One of our patients developed the disease after having received a total daily dose of 75 mg. for only two days, and another developed it after receiving an equivalent dose for a period of three days. In most of the patients jaundice developed between two and four weeks after initial administration of the medication. None of the 20 patients was known to have previously had liver disease.

Fourteen of these patients experienced an "influenza-like" syndrome, with chills, varying degrees of fever, malaise, nausea, and generalized muscular aching, prior to the onset of jaundice (Table 1). Coincident with or shortly after the onset of icterus, 16 patients experienced a moderate-to-severe

TABLE 1.—*Clinical Findings in Twenty Patients Having Chlorpromazine Jaundice*

Findings	Patients	
	No.	%
Jaundice	20	100
Pruritus	16	80
Hepatomegaly with tenderness	15	75
"Influenza-like" syndrome	14	70
Right upper quadrant pain or epigastric pain or both	11	55
Eosinophilia	8	40

degree of generalized pruritus. Eleven of the patients experienced some degree of right upper quadrant pain or epigastric abdominal discomfort or both early in their illness, but none described the "classic" pain of biliary colic.

On initial physical examination all patients were clinically jaundiced and 15 had slightly tender liver edges which were palpable 2 cm. or more below the right costal margin in the midclavicular line. The largest liver in this group of patients extended 6 cm. below the right costal margin.

On blood studies, none of the patients had anemia or platelet deficiency, and in all the total peripheral white blood cell count was within normal limits. Eight patients (40%), however, had a relative eosinophil count of greater than 8%, the highest noted being 30%. One patient, a 45-year-old white man who initially was thought to have an intra-abdominal malignant lesion, was noted to have a marked increase in eosinophilic elements in his bone marrow in addition to having a 6% peripheral blood eosinophil count. Bone marrow examinations were not performed in the remainder of the patients.

Liver-function studies consistently showed the pattern of an obstructive process rather than that of hepatocellular disease (Table 2). In all patients the initial serum alkaline phosphatase values were greater than 7.0 Bodansky units: In nine the levels were greater than 15.0, and the highest noted was 24.1. During recovery from the disease it was noted that this was the last of the liver-function tests to return to normal limits. The direct- and indirect-reacting bilirubin values were elevated in all patients and correlated well with the icteric indices and the degree of clinical jaundice. Sulfobromophthalein (Bromsulphalein) tests were not done during the icteric phase of the disease. Plasma total cholesterol and cholesterol ester values were determined in 12 of the 20 patients, and in all of these both values were found to be significantly elevated; the highest total cholesterol and cholesterol ester values recorded being 1010 and 626 mg. per 100 ml., respectively, in the same patient.

The results of studies that usually reveal abnormal findings in patients having hepatic cellular dysfunction were consistently normal or only slightly altered. In 19 patients results of repeated cephalin-cholesterol flocculation tests were negative; in 1 patient the result of this test was 1+ in 48 hours on two occasions. The zinc sulfate turbidity value was normal in all 10 of the patients in whom the test was utilized. The thymol turbidity test, on the other hand, yielded slightly elevated values in 6 of the 20 patients studied, but in none was it higher than 9.7 units. Total serum proteins, serum albumin, and serum globulin determinations were obtained in all patients, and in 17 they were normal. Three of the patients showed a reversal of the albumin-globulin ratio, but in none of these was the reversal marked. In all patients prothrombin times were done on several occasions, and in all instances they were found to be 14 seconds (100%).

The duration of jaundice and of abnormal results of hepatic-function studies varied considerably, the shortest period being 8 days and the longest 10 months (two cases). The usual duration was 28 to 40 days. Clinical improvement and an improvement in the patient's sense of well-being usually

TABLE 2.—*Findings on Liver-Function Tests in Twenty Patients Having Chlorpromazine Jaundice*

Factor	Evidence of Obstruction			Hepatocellular Damage			
	Alkaline Phosphatase	Serum Bilirubin	Plasma Cholesterol & Cholesterol Esters	Cephalin Flocculation	Zinc Sulfate Turbidity	Thymol Turbidity	Serum Protein
Cases tested	20	20	12	20	10	20	20
Cases with abnormal results	20	20	12	0	0	6	3

preceded the initial improvement noted in the laboratory studies.

One patient who had a prolonged clinical course was a 36-year-old laborer who underwent abdominal exploration because of a preoperative clinical impression of extrahepatic biliary obstruction. Findings at operation, including those on an operative cholangiogram, revealed the biliary tree to be entirely free from anatomic obstruction. A liver biopsy specimen taken at the time of operation showed marked intracanalicular bile stasis and plugging, with associated periportal cellular infiltration of the combined mononuclear and polymorphonuclear type—changes consistent with chlorpromazine jaundice. The postoperative course was unremarkable, but the patient remained jaundiced, with little change in the hepatic-function studies, until two months later, when he returned with the clinical picture of acute abdominal disease. At operation he was found to have an acute ulcerating hemorrhagic cholecystitis without evidence of calculi in the gallbladder or bile ducts. Again his postoperative course was essentially uneventful, but he remained clinically jaundiced for an additional seven months, after which time he recovered completely—all results of hepatic-function studies also returned to normal. The liver biopsy specimen obtained at the time of the second operation showed considerable regression in the degree of bile stasis and periportal infiltrate as compared to the initial biopsy specimen obtained two months previously. Whether the occurrence of such an acute ulcerating hemorrhagic cholecystitis in this patient was related to the chlorpromazine jaundice or merely coincidental with it is not known.

Two patients in this series were pregnant during the course of the chlorpromazine-induced liver disease. One, a 25-year-old woman, recovered completely within four weeks after onset of the jaundice, enjoyed excellent health throughout the remainder of her pregnancy, and uneventfully delivered a healthy normal infant at term. The other, a 34-year-old woman, was approximately six weeks pregnant when she was first seen at the Cleveland Clinic, and jaundice allegedly had developed two months before examination here. A needle biopsy of the liver revealed normal hepatic cells and portal spaces and marked intracanalicular bile stasis. Later, at operation, she was found to have no evidence of extrahepatic biliary obstruction. The operative liver biopsy showed changes identical with those of the original biopsy. Her postoperative course was unremarkable, but the icterus and altered results of hepatic-function tests persisted until approximately two weeks after delivery. The delivery was uncomplicated, and four months post partum she and her child were normal in every respect.

Follow-up data on all 20 patients presented in this paper indicate that eventual recovery from this drug-induced liver disease was complete in all.

Morphologic Changes

The histologic changes demonstrated in sections prepared from specimens obtained by needle biopsy should in most cases indicate the nature of the hepatic disease. The findings in each of two other conditions, infectious hepatitis and obstructive jaundice due to extrahepatic causes, may be confused with those in chlorpromazine jaundice. However, if careful attention is paid to the histologic changes and they are then correlated with the clinical findings, the diagnosis should be evident. Nineteen biopsy specimens from 15 of the 20 patients were available for diagnosis and further study. These tissues were carefully compared with those from patients having viral hepatitis or obstructive jaundice to delineate the differentiating features.

In general, in chlorpromazine jaundice, the architecture of the liver lobule remains intact. A total of 12 types of cellular change were studied and compared. Five of these separate changes were sought in the structure of the liver cells per se. These included the following changes:

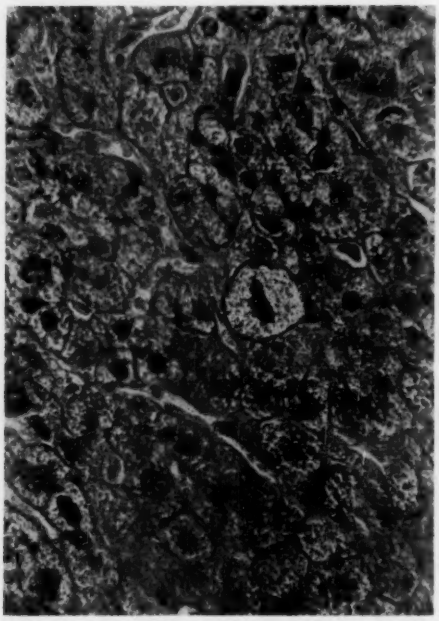


Fig. 1.—Single cell showing hydropic change with clearing of the cytoplasm and multinucleation. Masson stain; × 450.

1. "Balloon" degeneration of the liver cell, a rather marked hydropic change in the individual cell resulting in its appearing swollen and vesicular (Fig. 1). This change was found in 8 of the 19 specimens. It also is a prominent feature of viral hepatitis and is therefore of no value for differential diagnosis.

2. Multinucleation of the liver cell. This change was found in 18 of the specimens; the number of nuclei ranged from two to five. The change is present in both viral hepatitis and obstructive jaundice.

3. Necrosis of liver cells. Two types of necrosis were sought; the first is the Councilman type of necrosis, a special form represented by the presence of a small pyknotic liver cell with intensely oxyphilic cytoplasm and a darkly staining shrunken nucleus. This change occurred in only 1 of 19 specimens, and the absence of this finding is one of the major features in differentiating chlorpromazine jaundice from viral hepatitis. The particular patient with the change had a recent history of severe alcoholism. The usual type of necrosis of the liver cell was also sought, and it also occurred in only 1 of 19 specimens—the specimen from the same patient who had the other type of necrosis.

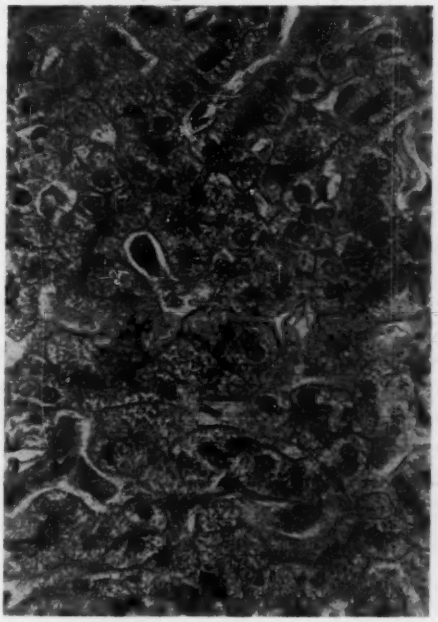
4. Fatty change was uncommon, but it occurred in five of the specimens.

5. Mitosis. Evidences of active proliferation of liver cells occurred as mitotic figures in liver cells in five specimens.

As a consequence, so far as liver-cell morphology is concerned, the absence of necrosis is one of the major features in differentiating chlorpromazine jaundice from viral hepatitis; necrosis occurred in the biopsy specimen from only 1 of 15 patients having chlorpromazine jaundice. In this one the liver may also have been damaged by his nutritional deficit (alcoholism).

Evidence of inflammation was also sought; it occurred in 10 of the 19 specimens. Inflammation was manifested by (1) a portal infiltrate of lymphocytes and histiocytes more intense than that usually seen, (2) a portal infiltrate of polymorphonuclear leukocytes, and, occasionally, (3) a portal infiltrate of eosinophils. The specimens from nine patients showed a polymorphonuclear infiltrate in the portal areas, and those from three had eosinophils as a portion of this reaction. The same type of infiltrate occurred in specimens from patients having viral hepatitis or obstructive jaundice.

Fig. 2.—Photomicrograph showing marked capillary bile stasis and bile pigment present in sinusoidal macrophages. Masson stain; × 450.



Evidences of obstructive phenomena that were sought in the 19 specimens included (1) capillary bile thrombi among the liver-cell cords—found in all specimens (Fig. 2), (2) bile duct proliferation of small hepatic ducts of slight degree—found in three specimens, and (3) large bile "lakes" and accumulations of pigment in larger bile ducts—found in none of the specimens. This absence of bile in the large ducts or as larger "lakes" is the major differentiating feature between chlorpromazine-induced liver disease and obstructive jaundice of large bile duct origin.

Kupffer cells also were studied for changes. Seventeen of the nineteen specimens showed sinusoidal macrophages stuffed with pigment. This phenomenon also occurred in specimens from patients having viral hepatitis or obstructive jaundice and was of no assistance in differential diagnosis.

Treatment

Treatment in all 20 of our patients was the same as that administered for cirrhosis: high-carbohydrate and high-protein diet, bed rest, and large doses of supplemental vitamins, particularly the B-complex. Some of the patients were given bile salts with the thought that bile might stimulate the flow of bile into the gastrointestinal tract and decrease the stasis of bile in the liver. Some were given antihistaminics because of the possibility that the reaction was allergic. It was difficult for us to determine whether any of these measures was of any definite help to the patients.

Five patients, including the two patients who had prolonged jaundice, were given adequate steroid therapy, including both corticotropin (ACTH) and cortisone, for minimum periods of one month. We were unable to determine that steroid therapy was of any benefit; it certainly did not alter the course in the patients with prolonged jaundice.

While it is difficult for us to determine any method of therapy that is effective, we believe that treatment of this condition should be similar to that of hepatitis. The bed rest, diet, and supplemental vitamins will at least minimize damage to the liver from the obstructive jaundice itself. While others have continued the administration of chlorpromazine even in the presence of jaundice or have given this medication again after the jaundice has subsided, we believe this may be dangerous. Shay and Siplet [16] reported one patient who reacted to a very small dose of chlorpromazine (5 mg.) months after she had recovered from jaundice induced by the drug. We show the tablets to our patients and caution them not to use them again.

Comment

The histories, clinical courses, alterations in results of hepatic-function tests, and changes in hepatic morphologic findings in our 20 patients having chlorpromazine liver disease are not unlike those previously described in the medical literature. The development of this entity seems to bear no relationship to the total daily dosage or to the duration of treatment with the drug. It is doubtful, also, that the route of administration influences the incidence of this problem.

As noted by Werther and Korelitz [17] in an analysis of 22 of their own cases and 27 cases from the medical literature, the disorder usually is initiated by an episode of systemic symptoms that occurs about two weeks after therapy with chlorpromazine has been instituted. Werther and Korelitz [17] also noted that significant peripheral eosinophilia occurred in approximately 66% of the patients, a figure somewhat higher than that noted in our patients, but they emphasize its occurrence early in the disease. Many of our patients had been jaundiced for a considerable period of time prior to their initial visit, a fact which may explain our relatively low incidence of peripheral eosinophilia.

The results of hepatic-function tests in those cases reviewed by Werther and Kore-

litz, as well as in those reported by others,[20, 22-25] consistently show the alterations indicative of an obstructive type of jaundice. As noted by Shay and Siplet,[16] the elevation of the serum alkaline phosphatase value is the first chemical abnormality noted in the patient with "liver sensitivity" to chlorpromazine, and therefore it is the most sensitive and accurate means of detecting impending hepatic dysfunction in those patients being treated with the drug. The findings of normal or only slightly altered results of tests of hepatocellular function in our patients are in complete agreement with the findings of those workers mentioned above.

The greatest problem in the diagnosis of any condition is to remain aware of its possibility. Chlorpromazine tablets are distinctive in appearance, and because of this one of us (C. H. B.) carries them in his pocket and shows them to every jaundiced patient he sees. This has been found to be most helpful. It also is possible for a patient who has taken chlorpromazine to develop obstructive jaundice from other causes, such as a common duct stone or a carcinoma of the ampulla of Vater or of the pancreas. Because of the latter possibility, operation may well be justified in some patients with all the clinical and laboratory signs of obstructive jaundice persisting for more than two to three months, even though they may have a history of chlorpromazine therapy.

The chief problem in differential diagnosis of chlorpromazine jaundice lies in excluding the possibility of extrahepatic biliary obstruction. Because chlorpromazine is widely used in all fields of medical practice, a constant alertness to the possibility of its being an offending agent must be maintained when one is evaluating any case of obstructive jaundice. An adequate history and a high index of suspicion should in most instances lead to a correct clinical diagnosis. It should then be possible in most cases to confirm the diagnosis by study of tissue sections obtained by needle biopsy of the liver. However, there will undoubtedly remain some cases in which a definite diagnosis can not be made without the benefit of laparotomy, cholangiography, and operative liver biopsy. Of our 20 patients, 6 were operated on for definitive diagnosis; most of these patients were operated on early in our experience with the problem and at a time when relatively little was known of the clinical and laboratory features of this syndrome.

Summary

Twenty patients with chlorpromazine jaundice have been studied, with liver biopsies being obtained in 15 of the 20. Six other patients were excluded because of incompleteness of study or insufficient follow-up.

All of the patients were jaundiced. Sixteen, or 80%, had pruritus; fifteen had hepatomegaly with tenderness; fourteen had an influenza-like syndrome; eleven had abdominal pain, and eight had an eosinophilia. The duration of administration of the drug ranged from 2 to 58 days. One patient received only 75 mg. daily for two days. Jaundice usually developed from two to four weeks after initial administration of the drug.

Liver-function studies consistently showed the pattern of an obstructive jaundice rather than of hepatocellular disease. The alkaline phosphatase, which seems to be the best test for this type of jaundice, was elevated in all 20 patients. Cholesterol and cholesterol esters were elevated in each of 12 patients in which these tests were done. Flocculation and turbidity studies (cephalin, zinc sulfate, and thymol) were uniformly normal, as were the serum proteins (albumin-globulin ratio and Tiselius proteins).

The duration of jaundice ranged from 8 days to 10 months (two patients). Two patients were pregnant during their jaundice, which seemed to have no effect on their pregnancies or the fetuses. Follow-up studies in all patients in this group indicated

eventual recovery without any residual liver damage.

Pathologic examination by liver biopsy (either at operation or with a Vim-Silverman needle) was done in 15 of the 20 patients. On the basis of findings on needle biopsy, an absence of necrosis of any type within the liver cells usually will serve to differentiate chlorpromazine jaundice from viral hepatitis, and the absence of the large accumulations of bile, either as lakes which may be previously dilated ducts or within larger ducts, serves to differentiate chlorpromazine jaundice from obstructive jaundice due to extrahepatic or large bile duct obstruction. The hepatic lesion produced by chlorpromazine, however, cannot be morphologically distingiushed from other drug-induced lesions, such as those induced by methyltestosterone ingestion.

Although no effective treatment was found, we believe that a "hepatitis regimen" should be prescribed for these patients, with a high-carbohydrate high-protein diet, bed rest, supplemental vitamins, etc. Steroid therapy was ineffective in five patients.

Reprint requests should be addressed to Dr. Charles H. Brown, Department of Gastroenterology, Cleveland Clinic, 2020 E. 93d St., Cleveland 6, Ohio.

REFERENCES

1. Van Ommen, R. A., and Brown, C. H.: Obstructive-Type Jaundice Due to Chlorpromazine (Thorazine): Report of 3 Cases, J. A. M. A. 157: 321-325 (Jan. 22) 1955.

2. Goldman, D.: Treatment of Psychotic States with Chlorpromazine, J. A. M. A. 157:1274-1278 (April 9) 1955.

3. Moyer, J. H.; Kent, B.; Knight, R. W.; Morris, G.; Dizon, M.; Rogers, S., and Spurr, C.: Clinical Studies of Anti-Emetic Agent, Chlorpromazine, Am. J. M. Sc. 288:174-189 (Aug.) 1954.

4. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine: New Inhibiting Agent for Psychomotor Excitement and Manic States, A. M. A. Arch. Neurol. & Psychiat. 71:227-237 (Feb.) 1954.

5. Azima, H., and Ogle, W.: Effects of Largactil in Mental Syndromes, Canad. M. A. J. 71:116-121 (Aug.) 1954.

6. Doughty, R.: Incidence of Jaundice Associated with Thorazine Therapy, Science Information Department, Smith, Klein, and French Laboratories, Philadelphia, August, 1955.

7. Myers, J. D.; Olson, R. E.; Lewis, J. H., and Moran, T. J.: Xanthomatous Biliary Cirrhosis Following Chlorpromazine, with Observations Indicating Overproduction of Cholesterol, Hyperprothrombinemia, and Development of Portal Hypertension, presented at the 17th Annual Meeting of the American Association of Physicians, Atlantic City, N. J., May 7, 1957.

8. Shay, H., and Harris, C.: Changing Concepts of "Xanthomatous Biliary Cirrhosis," Am. J. M. Sc. 223:286-300 (March) 1952.

9. Ahrens, E. H., Jr.; Payne, M. H.; Kunkel, H. G.; Eisenmenger, W. J., and Blondheim, S. H.: Primary Biliary Cirrhosis, Medicine 29:299-364 (Dec.) 1950.

10. Boardman, R. H.: Fatal Case of Toxic Hepatitis Implicating Chlorpromazine, Brit. M. J. 2:579 (Sept. 4) 1954.

11. Isaacs, B.; Macarthur, J. G., and Taylor, R. M.: Jaundice in Relation to Chlorpromazine Therapy, Brit. M. J. 2:1122-1124 (Nov. 5) 1955.

12. Movitt, E. R.; Meyer, M. A.; Snell, A. M.; Goldman, M. J.; Gibson, J. R.; Sullivan, B. H., Jr.; Webster, J. G., and Stone, R. B.: Jaundice Associated with the Administration of Chlorpromazine, SKF-2601-A (Thorazine): Report of 3 Cases, with Biopsies of the Liver, Gastroenterology 28:901-913 (June) 1955.

13. Menguy, R. B.; Bollman, J. L.; Grindlay, J. H., and Cain, J. B.: Biliary Stasis Produced by Chlorpromazine: An Experimental Study, Proc. Staff Meet. Mayo Clin. 30:601-606 (Dec. 14) 1955.

14. Sussman, R. M., and Sumner, P.: Jaundice Following the Administration of 50 Mg. of Chlorpromazine, New England J. Med. 253:499-502 (Sept. 22) 1955.

15. Gambescia, J. M.; Imbriglia, J.; Galamaga, P., and Winkelman, W., Jr.: Jaundice Associated with the Administration of Chlorpromazine, Gastroenterology 30:735-751 (May) 1956.

16. Shay, H., and Siplet, H.: Study of Chlorpromazine Jaundice, Its Mechanism and Prevention: Special Reference to Serum Alkaline Phosphatase and Glutamic Oxalacetic Transaminase, Gastroenterology 32:571-591 (April) 1957.

17. Werther, J. L., and Korelitz, B. I.: Chlorpromazine Jaundice: Analysis of 22 Cases, Am. J. Med. 22:351-366 (March) 1957.

18. Elkes, J., and Elkes, C.: Effect of Chlorpromazine on Behaviour of Chronically Overactive Psychotic Patients, Brit. M. J. 2:560-565 (Sept. 4) 1954.

19. Garmany, G.; May, A. R., and Folkson, A.: Use and Action of Chlorpromazine in Psychoneuroses, Brit. M. J. 2:439-441 (Aug. 21) 1954.

20. Cohen, I. M., and Archer, J. D.: Liver Function and Hepatic Complications in Patients Receiving Chlorpromazine, J. A. M. A. 159:99-101 (Sept. 10) 1955.

21. Pelner, L., and Waldman, S.: Chlorpromazine-Induced Jaundice, Case Report, Postgrad. Med. 18:349-353 (Oct.) 1955.

22. DeVore, J. K.; Daugherty, C., and Schneider, E. M.: The Effect of Chlorpromazine on Hepatic Function and Morphology, Gastroenterology 31: 391-398 (Oct.) 1956.

23. Kelsey, J. R., Jr.; Moyer, J. H.; Brown, W. G., and Bennett, H. D.: Chlorpromazine Jaundice, Gastroenterology 29:865-876 (Nov.) 1955.

24. Kreps, S. I.: Jaundice Associated with Thorazine Simulating Methyltestosterone Jaundice, New York J. Med. 55:2957-2960 (Oct. 15) 1955.

25. Weiss, L. B.; Fischbach, M. W., and Schloss, E. M.: Jaundice During Thorazine Therapy, J. Albert Einstein M. Center 3:91-95 (May) 1955.

Psychometabolic Changes in Phenylketonuria Treated with Low-Phenylalanine Diet

HANS MEYER, M.D.; EDWIN T. MERTZ, Ph.D.; HAROLD E. STADLER, M.D.; HENRY LELAND, Ph.D., and JOSEPH CALANDRO, M.T., Butlerville, Ind.

The extreme interest which has been shown in the use of special diet in the attempt to control or prevent nervous system degeneration associated with phenylketonuria may be due to the obvious fact that at present no other practical approach to the problem exists. The rather widespread discussion of the difficulties associated with treatment of the phenylketonuric has led to more extensive testing for the disorder and concomitant more accurate and early diagnosis.

Transmitted as a recessive hereditary trait apparently linked with blondism,[1] phenylketonuria results from the inborn failure of the organism to hydroxylate phenylalanine to tyrosine. The accumulated phenylalanine is partially deaminated in the kidney and excreted in the urine as phenylpyruvic acid, phenyllactic acid, and phenylacetic acid. The plasma concentration of phenylalanine in the normal human is approximately 1.4 mg. per 100 cc. Plasma levels of phenylalanine in the phenylpyruvic person are found to be 20 to 30 times that figure, and spinal fluid concentrations of phenylalanine parallel the high levels noted in the plasma. It is to be recognized that there is no relationship between the severity of the mental defect and the degree of phenylalanine concentration in the blood. The association of this defect in amino acid metabolism and the demyelination is constant, though a strict relationship has yet to be established.

A large number of workers in the field have elaborated diets which have originally been of the protein hydrolysate type in the attempt to eliminate foods containing phenylalanine. Modification of this diet became necessary, and foods containing small amounts of phenylalanine, such as milk, were added.

Several laboratories[2-6] have reported the use of a diet based upon a low-phenylalanine protein hydrolysate to control phenylketonuria in children. One practical disadvantage of this diet is the high cost of the hydrolysate. Assuming that this obstacle could be overcome by more economic manufacturing methods, there is the additional problem of the long-term treatment involved. We believe that we have been able to overcome the previous difficulty relative to the unpalatability.

Block, et al.[7] have shown that phenylketonurics synthesize the same tissue proteins as normal human beings. One would, therefore, expect that the phenylketonuric would fare best receiving a normal pattern of amino acids in his diet. The deleterious effects noted in animals when the normal amino acid patterns found in high-quality proteins are ignored have been emphasized by Elvehjem.[8] The use of a diet containing low levels of high-quality proteins seemed to us to be a more rational approach in view of these findings.

Submitted for publication Aug. 23, 1957.

Aided by a grant from the U. S. Public Health Service, National Institute of Neurological Disease and Blindness (677D).

The personnel of Muscatatuck State School Butlerville, Ind., aided in the completion of this study (Dr. Alfred Sasser, Jr., Administrator).

Muscatatuck State School, Consultant in Biochemistry (Dr. Mertz), Consultant in Pediatric Neurology (Dr. Stadler), and Chief of Laboratory Services (Mr. Calandro). Fort Wayne State School, Fort Wayne, Ind., Clinical Director (Dr. Meyer). Parsons State Hospital and Training Center, Parsons, Kan., Director of Psychological Services (Dr. Leland).

TABLE 1.—*Low-Protein Diet*

Breakfast	Lunch	Dinner
8 oz. liquid formula *	8 oz. liquid formula	8 oz. liquid formula
3½ oz. cornstarch dessert †	3½ oz. cornstarch dessert	3½ oz. cornstarch dessert
6 oz. orange juice	5 oz. fruit ‡	5 oz. fruit ‡
1 teaspoonful Homicebrin (homogenized multiple-vitamin preparation, Lilly)	5 oz. vegetable §	5 oz. vegetable §
Cornstarch cookies[18] ad lib.	Cornstarch cookies ad lib.	Cornstarch cookies ad lib.

* See text for preparation.
† To 2¼ oz. of dry cornstarch pudding add 8 oz. of liquid formula, cook to thicken, then add 3 gm. of mineral mix[18] and mix thoroughly. Rotate different flavors.
‡ Rotated pureed apple sauce, peaches, pears with pineapple, and apricots with apple sauce.
§ Rotated pureed beets, carrots, squash, and regular tomatoes.

The Diet

We have formulated a low-protein diet, the nature of which is summarized in Table 1. The liquid formula * is prepared by stirring 4 oz. (113.4 gm.) of a dry egg-whey mixture into approximately 25 oz. of water and adding 3 oz. of heavy cream (36% to 40% butterfat), 3 tablespoonfuls of dark Karo corn syrup, and 1 drop of vanilla extract, to give 1 qt. of finished liquid formula. This preparation is strikingly more palatable that that prepared with a protein hydrolysate. The dry egg-whey mixture (Shuman Chemical Laboratory, Inc.) contains in each 4 oz. the following: dry egg yolk solids, 15.2 gm.; dried whey solids, 43.0 gm.; glycine, 10.0 gm.; DL-methionine, 0.2 gm.; L-glutamic acid, 0.2 gm.; L-tyrosine, 0.2 gm.; sodium chloride, 0.7 gm., and dextrose 43.9 gm. Four ounces of the dry mixture supply approximately 470 kilocalories of energy and approximately 22 gm. of crude protein ($N \times 6.25$), including 10 gm. of egg-whey proteins containing 370 mg. of phenylalanine.

Two older children (Fig. 4) who were started on the diet (Subject 4, 9 yr. 9 mo., 20 kg., girl, and Subject 2, 12 yr. 3 mo., 30 kg., boy) consumed the diet as outlined in Table 1. One child (Subject 3, 4 yr. 1 mo., 14 kg., girl) consumed 24 oz. instead of the 32 oz. of liquid formula daily. It is estimated that Subjects 3 and 4 consumed on the average 35 mg. of phenylalanine per kilogram of body weight daily, whereas Subject 2 consumed on the average 25 mg. of phenylalanine per kilogram of body weight daily.

The National Research Council recommended allowances[9] were satisfied by this diet, with the exception of total protein intake. The diet outlined in Table 1 provided approximately 30 gm. of crude protein ($N \times 6.25$) daily, of which 13 gm. was of animal origin; 5 gm. of plant origin, and the remainder, free amino acids. It is generally assumed that nitrogen balance can be maintained in humans with a minimum of 0.5 gm. of high-quality protein per kilogram of body weight per day,[11] and this minimum requirement was met in all cases. However, the N. R. C. recommended allowance of 2 to 3 gm. of protein per kilogram of body weight daily was not satisfied by this dietary regimen. Realization of this recommendation would have raised the phenylalanine intake to an excessive level.

The diet outlined in Table 1 supplied daily not less than 3 gm. of sodium chloride, 1 gm. of calcium, 1 gm. of phosphorus, 15 mg. of iron, 2 mg. of copper, 2 mg. of manganese, and 150μg. of iodine in addition to the protein intake. Vitamin requirements were adequately provided for by the daily administration of Homicebrin (homogenized multiple-vitamin preparation, Lilly), 1 teaspoonful daily, and by the vitamins contained in the liquid formula, fruits, and vegetables.

The diet (Table 1) supplied about 1600 Cal. daily, exclusive of cornstarch cookies. Each cookie provided an additional 50 Cal.; these were fed when needed. The diet in Table 1 supplied an estimated 680 mg. of phenylalanine daily. The egg-whey dry formula provided 370 mg.; the heavy cream in the liquid formula, 150 mg., and the fruits and vegetables, 160 mg. of phenylalanine.

Recent studies by Paine and Hsia[16] suggest that the phenylalanine intake should

* Supplied by Shuman Chemical Laboratory, Inc., Box 543, West Lafayette, Ind.

not exceed 25 mg. per kilogram of body weight per day in the phenylketonuric. This intake was maintained in Subject 2 but was exceeded in Subjects 3 and 4. Nevertheless, Subject 4 showed one of the best responses to dietary treatment, in spite of a level of 35 mg. of phenylalanine per kilogram of body weight daily, a point which is discussed later. Replacement of the heavy cream in the liquid formula with an isocaloric amount of edible vegetable oil would have reduced the intake of Subjects 3 and 4 to approximately 25 mg. of phenylalanine per kilogram of body weight. This modification was not tested in the present report but has been found to be effective in studies on outpatients.

Methods

(*a*) *Metabolic (Laboratory).*—The effectiveness of the low-protein diet outlined in Table 1 was studied by selecting three pairs of children who demonstrated similar physical and mental development and functional efficiency. This group was assembled in a large room in our nursery and was under constant supervision of special personnel particularly interested in this study. The children were brought together two weeks before any dietary studies were started so that they could become accustomed to each other and to their new surroundings.

One member of each pair received the special diet. The control diet consisted of regular hospital fare, which supplied an estimated 50 to 80 gm. of protein and 2.5 to 4 gm. of phenylalanine daily. The special diet (Table 1) has been described in the previous section. Phenylpyruvic acid and creatinine were determined regularly in the morning urine specimens, and phenylpyruvic acid creatinine ratios were calculated.[8] These average ratios for the first five months are outlined in Figures 1, 2, and 3. Serum phenylalanine levels were determined on the six subjects at the end of the first and second months.[8] Total serum protein (grams per 100 ml. of serum) were determined after four and one-half months of study. During the last three weeks of the initial six-month period, the dried egg yolk solids in the liquid formula were replaced with a mixture of purified essential amino acids plus tyrosine and glutamic acid, which supplied each of the essential amino acids (except phenylalanine) in the amounts previously provided by the egg yolk solids. This reduced the crude protein content ($N \times 6.25$) from 22% to 19%; the animal protein content from 10 to 5 gm., and the phenylalanine from 370 to 185 mg. per 4 oz. of the dry mixture. This change reduced the phenylalanine intake of the child receiving the special diet to 350 to 700 mg. daily. At the end of the six-month period the diets of the three pairs of children were reversed for a period of two and one-half months (Shown in Figs. 1, 2, and 3).

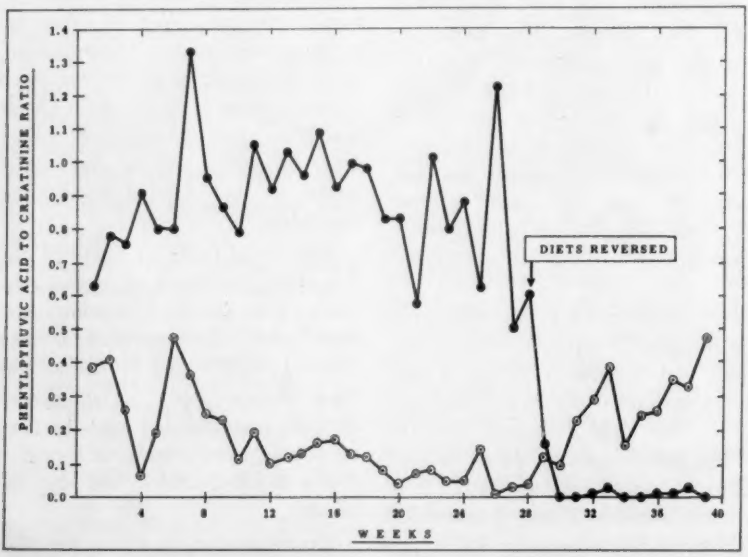


Fig. 1.—Line with solid circles indicates Subject 6; that with open circles, Subject 4.

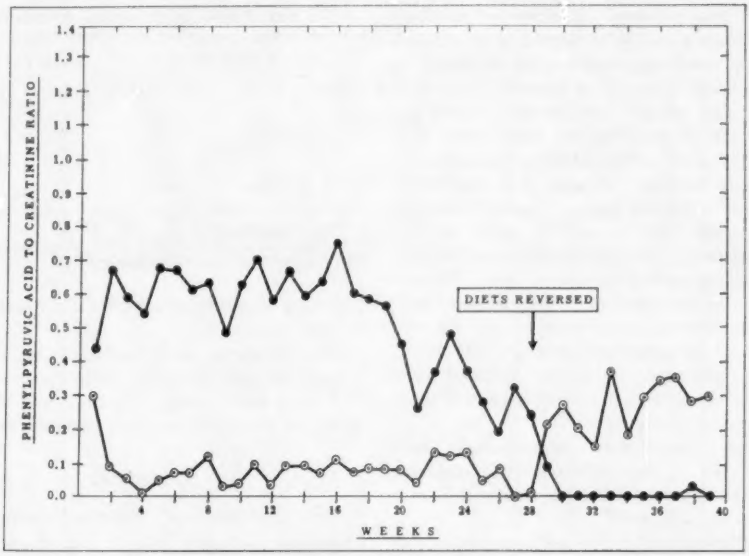


Fig. 2.—Line with solid circles indicates Subject 5; that with open circles, Subject 2.

Changes in the phenylpyruvic acid to creatinine ratio for the two and one-half months reversal period are also shown in Figures 1, 2, and 3.

Urinary Phenylpyruvic Acid: Initial identification of phenylketonurics in the population of the institution was made by screening urine specimens of all admitted patients with the ferric chloride test.[19] Quantitative phenylpyruvic acid values were determined by a modification of the phenylhydrazone method of Penrose and Quastel.[22] We found significant differences in the "color value" of normal urine samples from different persons and even from the same person when the urinary creatinine concentration increased. The "color value" of the urine increased as the creatinine concentration increased. An attempt was made to

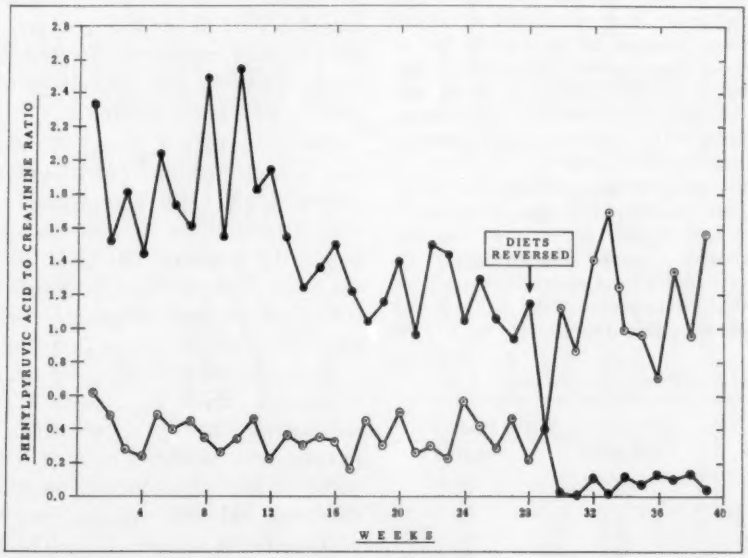


Fig. 3.—Line with solid circles indicates Subject 1; that with open circles, Subject 3.

circumvent this problem. A series of dilutions was made from a sample of normal urine containing a high creatinine concentration to result in descending levels of creatinine content. These dilutions were then treated with phenylhydrazine and alkali and the colors compared with known concentrations of pure sodium phenylpyruvate treated in the same fashion. It was thus possible to construct a correction curve relating creatinine (milligrams/100 ml.) in normal urine to that amount of phenylpyruvic acid (milligrams/100 ml.), providing an equivalent amount of color. Phenylketonuric urine specimens were then compared with pure sodium phenylpyruvate solutions and the total milligrams of phenylpyruvic acid per 100 ml. of urine was calculated. A correction based upon the variable concentration of creatinine was made possible by this technique.

Creatinine: Quantitative determinations were made with use of the Jaffe reaction, comparing the color developed in the urine sample against a pure creatinine standard.[13]

Serum Phenylalanine: One milliliter portions of serum were treated with five milliliters of 10% trichloracetic acid; the precipitate was sedimented by centrifugation and washed twice with one milliliter portions of trichloracetic acid. The original supernate and washings were combined and analyzed for phenylalanine by the Block and Bolling modification of the Kapeller-Adler method.[14]

(*b*) *Psychological.*—The experimental group was evaluated psychologically one month before the experiment started. Instruments used were the Vineland Social Maturity Scale, the Columbia Test of Mental Maturity, and the Wallin Peg Boards. The groups were reevaluated at the end of the six-month period and again at the end of the additional two-and-one-half-month period (Fig. 3 and Table 3). Observation notes were kept as to behavior and interpersonal relationships.

(*c*) *Clinical.*—The children were observed closely during the entire study period. Even the most trivial tendency to seizures, respiratory infections, and possible dietary deficiencies were charted. Medications were confined to the barest minimum in order to avoid a possible interference with results. Careful observations of height, weight, and other physical changes were noted and recorded. Electroencephalographic tracings were made at the beginning and termination of the six-month study (Table 4).

The attendants were instructed to record the amount of food eaten by both the experimental and the control group. No child was allowed to leave the room without close supervision.

TABLE 2.—*Serum Phenylalanine Levels*

Subject	Phenylalanine, Mg/100 Mg. Serum	
	End 1st Mo.	End 2d Mo.
5 (control)	47	32
2	7	12
6 (control)	47	33
4	17	10
1 (control)	37	30
3	17	12

TABLE 3.—*Psychological Evaluation*

Subject	I. Q., C. M. M. S.		Wallin Peg Board †	
	Before	After 6 Mo.	Before	After 6 Mo.
4*	NT	26	—	+
3*	NT	NT	—	+
2*	NT	20	—	+
5	NT	NT	—	—
6	25	24	+	+
1	NT	NT	—	—

* Group receiving diet.
† — indicates a refusal to try test or even handle pegs and board; + indicates some attempt to perform.

Comment

(*a*) *Biochemical Data.*—Desirable biochemical response to the low-phenylalanine diet can be assumed to have been approached when the ratio of phenylpyruvic acid to creatinine (in morning specimens of urine of treated patients) is 25% or less of that found in the control patient of the same age (Figs. 1, 2, and 3). Armstrong and Taylor[3] have shown that a satisfactory correlation exists between the phenylpyruvic acid-creatinine ratio of a random sample of urine, the serum phenylalanine levels, and the total daily nitrogen and phenylpyruvic acid excretion. Twenty-four-hour urine specimens are difficult to obtain in patients with phenylketonuria.

Our data (Figs. 1, 2, and 3) indicate that the average weekly phenylpyruvic acid-creatinine ratio for both treated and untreated children varies with the age of the child; the younger the child the higher the ratio. Thus Subject 1 (4-year-old control) had an average phenylpyruvic acid-creatinine ratio of 1.6 the first five months, whereas Subject 5 (12-year-old control) had a ratio of only 0.58. Subject 6 (10-year-old control) had an intermediate phenylpyruvic acid-creatinine ratio of 0.91. This variation was also observed in the treated children, and the average phenylpyruvic acid-creatinine ratios of 0.35, 0.18, and 0.08 were obtained during the first five months

TABLE 4.—*Clinical Observations*

Subject	Diet or Control	Date	Wt., Lb.	Ht., In.	Nutritional Status	Skin & Hair	Eyes	Motor Development	Seizures	C. N. S.	E. E. G.	Remarks
	D	7/1/56	27½	40	Asthenic	Brown	Dark	Sits	0	Gen. increase tonus	Dys. I	Clubfeet
3	D	1/11/57	30	40½	Improved	Dull gray	More alert	Rolls over	0	Gen. increase tonus	Within normal limits	Clubfeet
	C	3/12/57	31	40½	Improved	More brown	More alert	Does not attempt to	0	----	Dys. III	Clubfeet
	C	7/1/56	32	39	Sl. asthenic	Blond	Blue	Sits	0	Gen. increase tonus	Within normal limits	----
1	C	1/11/57	33½	39	Much improved	Little change	More alert	Tries to stand	0	Gen. increase tonus	Within normal limits	----
	D	8/12/57	35	39	Much improved	Little change	More alert	Same	0	Gen. increase tonus	Within normal limits	----
	D	7/1/56	34½	45½	Poor	Light brown	Blue	Bed-ridden	6	No pathological reflexes	Dys. III	Only "simian" posture in group
4	D	1/2/57	40½	45½	Better	Dull gray	Listless	Simian posture	0	No pathological reflexes	Dys. II	----
	C	8/12/57	43	45½	Good	More brown	Alert	Walks freely	0	No pathological reflexes	Dys. II	Clonus, L. leg
	C	7/1/56	71½	52½	Good	Light brown	Blue	Walks freely	6	No pathological reflexes	Dys. III	Changed hair color & had seizures, while control patient
6	C	1/11/57	77½	55½	Fair	Striking change	Listless	Walks freely	0	No pathological reflexes	Dys. III	
	D	1/25/57	73½	56	Fair	Striking change	Listless	Walks freely	2	No pathological reflexes	Dys. III	
	D	7/1/56	70	50	Good	Dark brown	Brown	Withdrawn; sits, lies down	4	Gen. increase tonus	Dys. III	Clubfeet
2	D	1/11/57	73	52	Good	Striking change	Unchang.	Walks freely	3	Gen. increase tonus	Dys. II	Clubfeet
	C	3/25/57	77½	52	Good	Striking change	Unchang.	Picks up toys	0	Gen. increase tonus	Dys. II	Clubfeet
	C	7/1/56	58	52	Asthenic	Dark blond	Blue	Walks freely	0	No pathological reflexes	Dys. II	----
5	C	1/11/57	64	54	Good	Dark blond	Blue	Walks freely	0	No pathological reflexes	Dys. II	----
	D	3/25/57	61½	54	Good	Striking change	Listless	Walks freely	0	L. facial paresis	Dys. I	L. facial paresis still present

on the 4-, 10-, and 12-year-old children, respectively.

The reason for the variation of the phenylpyruvic acid-creatinine ratio with age is not known. One possible explanation is the increase in creatinine per kilogram of body weight with age and the decrease in excretion of creatinine (not measured by the Jaffe reaction) with age. It is also possible that in younger children a larger proportion of the ingested phenylalanine is metabolized via phenylpyruvic acid, whereas in older children alternate pathways become more prominent. Further studies should yield clarification of this interesting finding.

The biochemical data (Figs. 1, 2, and 3) also suggest that a lag period follows a period of low protein ingestion. The phenylpyruvic acid-creatinine ratio (during this lag period) remains at a relatively low level even though the child is rather suddenly given a large increase in protein intake. Subject 4 was given a high-protein diet for two and one-half months, after a six-month period of low protein intake. Her phenylpyruvic acid-creatine ratio was 0.1 for the first two weeks and 0.39 for the last two weeks of that two-and-one-half-month period. This lag period may be evidence of repletion of labile protein stores due to luxury consumption of protein. It is also possible that the tissues must adjust to higher levels of phenylalanine and that a period of time is required for effective conversion of excess phenylalanine to phenylpyruvic acid and similar abnormal metabolites. Additional studies of serum and urinary phenylalanine levels are needed to clarify this matter.

Serum phenylalanine levels were determined on the six subjects at the end of the first and second months (Table 2). Total serum protein levels (grams/100 ml. of serum) determined at the end of four and one-half months were as follows: Subject 5 (control) had 7.1; Subject 2 had 6.3; Subject 6 (control) had 7.1; Subject 4 had 5.1; Subject 1 (control) had 6.5; Subject 3 had 6.8. Satisfactory weight gains were achieved in all patients but one.

(*b*) *Psychological Characteristics.*—Generally speaking, the six children chosen for this experiment had most of the characteristics usually thought to be present in phenylketonuria. Most of them were blond-haired and blue-eyed and also had blue sclerae. Four of the six had obvious cranial and developmental anomalies. One of the patients was an active epileptic before the research period began and, in addition to two other patients, had a history of seizures during the experiment. All were considered severely mentally retarded (Table 3); none of them were toilet trained, and none could feed or dress themselves, though one of the patients had made good progress in this direction. Speech was absent, as was any communication within this group of children. All of them exhibited many of the characteristics commonly associated with childhood schizophrenia. They would sit and rock; they would beat their heads with their fists, their knees, or against the wall, and some would bite or otherwise mutilate themselves. There was consistent pattern of increased tension, increased psychomotor activity, and general hostility and destructiveness. These latter were almost always aimed at themselves, to the complete exclusion of other patients.

On the other hand, developmentally, while they seemed somewhat retarded physically, they were, for the most part, able to walk, climb stairs, to grasp with their hands, to chew, and to do many of the other things which come under the heading of development in locomotion and general self-help. One gets a general pattern of severe social and mental retardation in an otherwise physically able body. There were two exceptions to this—one being the girl with the consistent pattern of epileptic seizures, and the other a girl with some indications of spasticity (this patient had originally been given the diagnosis of cerebral palsy, spastic type, before it was discovered that she was phenylketonuric).

The patients were matched as closely as possible for age and functional levels, with the major emphasis being placed on age, since it was generally felt that it would be more practical to attempt this experiment with younger patients. However, since the sample is too small to be treated statistically and since the limited number of cases available made proper matching impossible, it was decided that each case be analyzed individually. Thus, the matching only serves the purpose of establishing a subject and a control.

The wide scatter of ages for the six subjects made it almost impossible to administer a psychometric test which on one hand would be equally valid for all six and on the other hand would produce scorable results. The attempts with the Stanford-Binet produced results in only half of the cases. The patients were too old for many of the developmental-type tests, and it was felt very strongly that the only tests which should be used were those which had been standardized on a similar age group. Some of the previous searchers [1] in this field failed to follow this rule and were thus able to report I. Q. improvements which were due to maturation and developmental change rather than to actual changes in the process of mentation.

It was finally decided that the Vineland Social Maturity Scale would be the best single instrument for measuring developmental changes and that the Wallin Peg Boards and the Columbia Test of Mental Maturity would give a fair estimate of mental changes. The results of this testing can be seen in Figure 4 and Table 3. It will be noted that the pattern of I. Q.'s, where available, differs quite a bit from the pattern of S. Q.'s. These latter are lower, and, even in the instances where an I. Q. score could not be had, the examiner feels that a mathematical interpretation of the available material would produce scores higher than the listed S. Q.'s for the same patient. This further fortifies the position that I. Q.'s derived from infant developmental scales are not valid for older children, regardless of mental age. The results on the Wallin Peg Boards are based on the willingness of patient to follow instructions and on the patient's attempt to complete the test. Actually, in no instance, either before or after the six-month period, was the test completed in a scorable manner. The test is more a measure of cooperation and trainability in this instance than of mental age or I. Q. For this reason, Table 3 indicates the results on a plus or minus basis, depending on the reaction of the child to the test. The Wallin Test and the Columbia Maturity Scale taken together, however, do give some picture of mental activity from which one can conclude that the diet seems to release latent ability.

A general analysis of the Figure and the Table reveals a very uneven pattern of development, with some slight improvement in the group receiving the diet and additional improvement in the control group when they were given the diet. Thus, we can conclude that the diet does bring about some measurable change, but the numbers would have to be increased greatly before we would have any idea whether or not this change was significant. (We would suspect, though, that it was not.)

In the area of functional efficiency, however, there were some very definite changes noted by the observers working on the research. For the purposes of this research, functional efficiency is thought of in terms of what the patient does on a day-to-day basis, how he behaves generally, and how he occupies his time, rather than what he is able to do in terms of potential or capacity. Thus a patient who may be able to feed himself but who sits and rocks all day would be considered on a lower level of functional efficiency than a patient who could not feed himself but who occupied himself in a more social way and who made an effort to learn. Many of the previously described autistic symptoms either disappeared or abated in the group given the diet, while there was no noticeable change in this area in the control group. Even

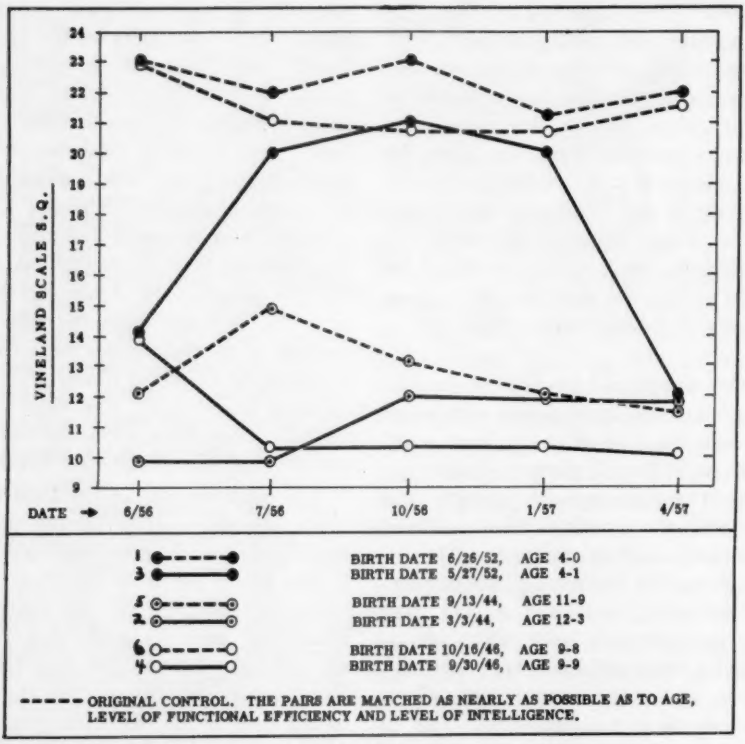


Fig. 4.—Numbers in explanation below chart are subject numbers.

those members of the control group who originally showed some developmental improvement by being placed in the protective and understanding environment of the nursery (Fig. 4) did not show any change in level of functional efficiency, with the exception of one patient who demonstrated what might possibly be called deterioration. In this instance the record speaks of a higher level of social development than in the case of the other patients in the experiment. He had been in a colony with patients who were functioning on a much higher level and had as a result picked up some habits of play and "social behavior." The change in environment in this case seemed to be the major factor in that when he was placed with the other children in the experimental group he "forgot" some of these former abilities and thus appeared to more closely resemble the rest of the group in the latter stages of the experiment.

The changes in functional behavior seem in most instances to follow a pattern of hills and valleys; i. e., there are periods when there is a total cessation of the autistic type of behavior and there are periods of decreased socialization and return to autism. However, even during the period of return the behavior is less pronounced and more controllable and the patient responds more readily to outside stimulus. During the periods of improvement the patient is much more willing to cooperate and to obey instructions. One of the patients began to use some speech; the rapidity and severity of the epileptic seizures in the patient who was prone to them was reduced, and all of them demonstrated a greater awareness of their peers and of the staff. When the diet was discontinued in this group there was an almost immediate return to the previous low level of functional efficiency, while the previous control group, who were then given

the diet, began to show some of the signs of improvement described above. For example, one of the boys before he was made part of the experimental group would sit and rock all day, doing very little else. After he received the diet, he began to walk around the room, to play with the other children, etc. When he no longer received the diet he returned to his previous behavior of sitting and rocking all day, and when given the diet again at the end of the experiment he began to show the improvement that had been indicated previously.

One further point of observation is that all of the patients, those who were not receiving the diet as well as those who were, responded very well to the increased attention which was afforded them by being placed in the nursery. There were sufficient differences, as have been indicated above, to enable it to be said that the major changes were probably due to the diet, but it must be remembered that some of the changes were probably due to the increased attention and that any further programming in this area should take both of these factors into consideration.

Summary and Conclusions of Psychological Fndings: The six patients in the experimental group, while all showing very definite individual characteristics, demonstrated sufficient consistency for us to gain certain insights. These points seem to be valid and in spite of the smallness of the sample can probably act as a guide for work in this area. The patients were measured in terms of physical and mental development and functional efficiency. The physical development has been discussed in another place in this paper. There were no major changes in mental development. It is felt that the changes reported by other searchers in th.s area were due to a confusion of concepts and that changes due to the normal maturation of the phenylketonuric patient [15] which were accelerated due to the diet were credited as being changes in I. Q. It is felt rather that the phenylketonuric patient is also burdened with a number of congenital anomalies which are probably irreversible and which thus make any major changes in mentation highly questionable. However, the pattern of social maturation is accelerated and the patient can be more readily trained to complete developmental tasks, and this would yield a very excellent prognosis from the point of view of the rehabilitation or rather habilitation of the phenylketonuric.

It is in the area of functional efficiency that the greatest changes were noted. In this area there were sufficient behavioral changes for one to conclude definitely that the diet greatly reduces the problem of management in these patients. This agrees with the findings of Paine et al.,[17] who used a low-phenylalanine hydrolysate. It is felt that for some reason phenylketonuria seems to produce symptoms similar to those found frequently in the autistic or schizophrenic child. There seems to be no adequate psychological explanation for this at this time, but it can be concluded from this experiment that regardless of cause the major area of improvement lies in the clearing of many of these autistic symptoms. We indicated above that the increased attention and specific developmental training would seem to be the best formula for the rehabilitation of the phenylketonuric patient.

(*c*) *Clinical Changes.*—It is very true that one may under certain circumstances be correct in the purely clinical diagnosis of phenylketonuria. A positive diagnosis, however, must rest upon laboratory confirmation. There are certain physical and constitutional qualities seen in the phenylketonuric which are typical yet not specific for the disease. The same situation prevails with regard to neurological findings. We had, for example, ignored acrocyanosis as an important sign, since we had observed it in practically every disease process witnessed in our institution. The most extreme degree of acrocyanosis was seen in the Mongoloid group as related to sudden weather variations. Hypertonicity was observed to vary a great deal even in the same patient

at periodic examinations. Associated congenital defects (microcephaly, clubfeet, etc.) would modify the growth and development of the person.

Anorexia accompanies cerebral damage very often, and the same is true of vomiting, febrility, and irritability. Changes indicative of dietary deprivations are manifest in institutionalized patients regardless of basic disease process. It is fundamental to medical doctrines that a regimen must be regarded from its capacities to accomplish good as well as to produce deleterious effects.

The adjustment of our patients to the new regimen was a difficult one. This observation was even more striking when the diets of the study pairs were reversed on Jan. 15, 1957. One of our original control patients (Subject 5) became irritable and tired very easily, and two weeks later he manifested a left facial paresis which is still apparent. Another patient (Subject 6) lost 4 lb. and presented a pathetic appearance. His weight is still 4 lb. below the original level, although he has become more active and alert.

Dull or ashen discoloration of the hair occurred in all special-diet patients, accompanied by lessening of the silken quality. Paradoxically enough, the hair of one of the control patients underwent identical changes. One patient developed a peculiar lipochromic eruption over the hands, feet, and buttocks. The discoloration of the areas was preserved in the plastic name band long after it disappeared spontaneously without treatment or change in regimen.

Skin pallor did not appear in any of the children during the study. The hemoglobin was found to increase from 0.15 to 1 gm. in four patients and 2 gm. in one patient. The hemoglobin of the latter patient rose from 9.1 to 11.7 gm.

Three patients had seizures which the electroencephalographic tracings had predicted. The subject whose hair changed color while he was a control was the only one who had seizures during the control period.

Pretibial edema developed on Dec. 14, 1956, in the patient whose adjustment to the new regimen was the most difficult of all. Rectal feedings were resorted to on a number of occasions in order to insure intake of his allotment of protein. One other patient developed mild edema of the hands.

Subject 4 showed the most outstanding improvement. This 10-year-old girl was bedridden, cachetic, and apathetic at the beginning of the study. She could not even sit or turn over without assistance. She now walks easily, picks up toys, and verbalizes. We must regard her progress during the six-month observation period as dramatic, since her period of stay at the State School (admitted January, 1952) had been marked by progressive deterioration.

General Conclusions and Interpretations

We feel rather strongly that the dietary approach to the fully developed state of phenylketonuria is a mandatory step, which while not routinely leading to definite general improvement in the afflicted does lend to them a sense of well-being and increased motor activity heretofore not accomplished. The children with whom we were involved all presented a full-blown picture of demyelinization; it is fully obvious that greater effects would have been noted had the regimen employed been instituted during the initial few weeks of life. Two problems continue to present themselves. The first has to do with recognition of the pure phenylketonuria. The modifying effects of associated congenital defects and anomalies must be reckoned with. One patient under study by one of us (H. E. S.) several years ago showed fusion of the anterior fontanel with O. F. circumference of 37 cm. at the age of 9 months. The child weighed 19 lb. and was 29 in. long at that time. Treatment would probably have been disappointing.

The other problem has to do with irreversibility. There is no answer to the

question as to what age is the critical period following which time the therapeutic effect would be questionable.

The results of our study were encouraging enough to lead to routine administration of the low-phenylalanine diet to all of our phenylketonurics who are under 15 years of age.

5508 E. Washington St., Indianapolis 19 (Dr. Stadler).

REFERENCES

1. Stadler, H. E.; Meyer, H., and Leland, H.: Phenylpyruvic Oligophrenia in a Mulatto, J. Nerv. & Ment. Dis. 124:205-207, 1956.

2. Woolf, L. I.; Griffiths, R., and Moncreiff, A.: Treatment of Phenylketonuria, with a Diet Low in Phenylalanine, Brit. M. J. 1:57-64, 1955.

3. Armstrong, M. D., and Taylor, F. H.: Studies on Phenylketonuria: I. Restricted Phenylalanine Intake in Phenylketonuria, J. Clin. Invest. 34:565-580, 1955.

4. Jervis, G. A.: Phenylpyruvic (Phenylketonuria), in Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns, A. Res. Nerv. & Ment. Dis., Proc. (1953) 33: 259-282, 1954.

5. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria, J. A. M. A. 161:1628-1630, 1956.

6. Blainey, J. D., and Gulliford, R.: Phenylalanine-Restricted Diets in the Treatment of Phenylketonuria, Arch. Dis. Childhood 31:452-466, 1956.

7. Block, R. J.; Jervis, G. A.; Bolling, D., and Webb, M.: Chemical and Metabolic Studies on Phenylalanine: III. A Note on the Estimation of Phenylalanine, J. Biol. Chem. 134:567-572, 1940.

8. Elvehjem, C. A.: Amino Acid Imbalance, Fed. Proc. 15:965-970, 1956.

9. Recommended Dietary Allowances, Food and Nutrition Board, National Research Counsel Publication 302, 1953.

10. Følling, A.: Über Ausscheidung von Phenylbrenztraubensäure in de Harn als Stoffwechselanomalie in Verbindung mit Imbezillität, Ztschr. physiol. Chem. 227:169-176, 1934.

11. Allison, J. B.: Nitrogen Balance and the Nutritive Value of Proteins, J. A. M. A. 164:283-289, 1957.

12. Penrose, L., and Quastel, J. H.: Metabolic Studies in Phenylketonuria, Biochem. J. 31:266-274, 1937.

13. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 13, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1954.

14. Block, R. J., and Bolling, D.: The Amino Acid Composition of Proteins and Foods, Springfield, Ill., Charles C Thomas, Publisher, 1951.

15. Leland, H.: Some Psychological Characteristics of Phenylketonuria, Psychol. Rep. 3:373-376, 1957.

16. Paine, R. S., and Hsia, D. Y. Y.: The Dietary Phenylalanine Requirements and Tolerances of Phenylketonuric Patients, A. M. A. J. Dis. Child. 94:224-230, 1957.

17. Paine, R. S.; Quinn, K. V.; Mautner, H., and Hsia, D. Y. Y.: A One-Year Controlled Study of the Effect of Low Phenylalanine Diet on Phenylketonuria, A. M. A. J. Dis. Child. 94: 429, 1957.

18. Clark, H. E.; Mertz, E. T.; Kwong, E. H.; Howe, J. M., and DeLong, D. C.: Amino Acid Requirements of Men and Women: I. Lysine, J. Nutrition 62:71-82, 1957.

Hypoxia of Abnormal Physiologic Origin as the Final Common Pathway in Gastroduodenal Ulcer Genesis

LIEUT. COL. EDDY D. PALMER (MC), and LIEUT. COL. JACQUES L. SHERMAN Jr. (MC), U. S. Army

In this era, thinking about the problem of gastroduodenal ulcer genesis is likely to prove more profitable than investigation. The investigative work has been prolific for more than a century, and, if enthusiasm, expense, and man-hours spent are factors which bear on the success of research, it is fair to assume that the answer is already in, unrecognized as such, among the archives. It cannot be said, however, that the history of ulcer research has been marked by especially productive synthesis of the great mass of clinical, pathologic, and pathophysiologic information which has turned up. Continuous review of available data in the light of new concepts is of paramount importance in ulcer research.

The following summarizes current understanding of the anatomy and physiology of the native arteriovenous shunt system of the gastroduodenum, the mechanism which controls mucosal blood flow, as they may pertain to the genesis of gastroduodenal ulcer. It is thought that the tremendous implications of shunt activity as the possible final common pathway for ulcer genesis have not been sufficiently exploited by those who have actually carried out the investigative work on the structures. Discovery of the shunt system of the gastrointestinal tract has permitted more definitive thinking about mechanisms whereby altered circulatory function may control the development of both local and diffuse gastrointestinal mucosal disease, including, in addition to gastroduodenal ulcer, ulcerative colitis and, perhaps, common gastritis, erosive esophagitis, and pseudomembranous enterocolitis.

Submitted for publication Oct. 15, 1957.

From the Medical Services, 2nd General Hospital, APO 180, and 2nd Field Hospital, APO 108, New York.

Anatomy of Shunts

Anatomically, the arteriovenous shunts of the esophageal, gastric, duodenal, small intestinal, and colonic walls seem very similar to those of the other organs of the body. Because the stomach has been most thoroughly studied in this regard, some features are known for gastric shunts which have not yet been proved for the other gastrointestinal organs. There are, naturally, several areas of interpretational disagreement among the people who have investigated the structures, but these have not contributed any degree of actual confusion. For a summary of current anatomic knowledge of the shunts throughout the body, one should consult the second edition of Clara's [20] wonderful monograph.

Normally in the gastroduodenal wall an arteriovenous shunt arises from each mucosal artery, either just before or just after the artery pierces the muscularis mucosae following its short course from origin in the submucosal arterial network. There is little difference in the concentration of shunts in various parts of the stomach and duodenum,[5] although several observers [19,26,27,56] have concluded that there is a unique pattern to the spacing of the mucosal arteries along the lesser gastric curvature and the posterior wall near the cardia. This point of confusion over the arterial supply of the stomach is the only major one which has persisted since Hofmann and Nather [34] and Djørup [27] so beautifully proved the absence of gastric end-arteries. It is created by the fact that the mucosal arteries in the region

of the gastric lesser curvature do not arise from the submucosal arterial plexus, although they freely communicate with it, but take their anatomic origin directly from the right and left gastric arterial chains.

Each shunt which lies in the vicinity of the muscularis mucosae operates to circumvent the large mucosal capillary bed which its mucosal artery normally supplies. The capillary bed per mucosal artery is believed to average about 1 cm. in diameter. The shunt segment bridges across to the vein which drains the capillary unit of the artery.

In addition to the shunts which lie on either side of the muscularis mucosae, there are many large shunts in the gastric subserosa. De Busscher [19] was impressed with their numbers and found them especially easy to study.

Two anatomic types of shunt exist in the esophageal,[22,49,63] the gastroduodenal, and the small and large bowel [20] walls—the direct and the indirect. An apparent disagreement over which is the commoner in the gastroduodenum is explained by misinterpretation by Barlow and colleagues [5] of de Busscher's [19] classification.

The direct shunt, the less common of the two, consists merely of a relatively short arteriovenous communication equipped with a pseudosphincteric closing mechanism of muscle cells. The arterial end of the communication is usually a branch of a mucosal artery, although occasionally it arises directly from a main limb of the submucosal arterial plexus. After a short course of variable tortuosity, the arterial segment widens to open directly into a mucosal vein or, occasionally, into a vein of the submucosal plexus.

The indirect type of shunt has a distinct, anatomically specialized channel between the arterial and venous sides. When studied histologically, the diameter of the channel seems to be only about 30μ, but the functional diameter is known to be about five times this figure. Arising from a mucosal artery, the arterial part of the shunt segment carries with it intima, a double muscle layer, and adventitia. There is no elastica. In the specialized intermediate segment, where arterial features predominate, the muscle cells give way to large layered epithelioid cells, the cells (*Quellzellen*) of Schumacher.[58] These cells have no contractile powers but are able to open and close the shunt lumen by quickly extruding and imbibing fluid.[59] The course of the intermediate segment, which is easily identified although not followed on ordinary histophathologic sections, may be very tortuous. Its lumen suddenly enlarges as it joins the venous part, and the Schumacher cells disappear. The shunt empties into either a mucosal or a submucosal vein. The specialized segment is surrounded by an adventitial nerve net, which is a continuation of the arteriolar plexus and which continues on to join the submucosal venous plexus. Nerve fibers in close association with the endothelial cells of the shunt segment have been described.[55]

In addition to the shunts, there is found in the gastric and duodenal mucosa an occasional direct terminal arteriovenous anastomosis, often close to the mucosal surface. These have no intermediate canal or capillary connections, nor do they seem to have the ability to obliterate their lumen.

It is not clear where the "cushioned arteries" (*Polsterarterien, artères à coussinet*) and "blocked veins" (*veines d'arrêt*) fit into the scheme of the shunt system.[31,33,64,65] They have been described by some investigators only in human stomachs which are diseased, but others have used the term *Polsterarterien* to describe normal shunt segments or certain artifactual mural invaginations, thereby creating the confusion. While making a simple histopathologic study of 112 stomachs resected for ulcer, Herzog [31] found arteriovenous shunts near the ulcers and, in addition, described cushioned arteries and blocked veins in the area. The former appeared to have sphincter-like longitudinal cell bundles in their walls, and these had protruded into the vessel lumen "like cushions" to block it. Upon reviewing more than 300 stomachs resected for ulcer,

Herzog [33] concluded that in many cases the finding formerly looked upon as endarteritis obliterans in ulcer stomachs actually represented degenerate forms of cushioned arteries. Functional observations on these structures are required before their significance can be determined.

Physiology of Shunts

Current understanding of the physiology of gastrointestinal shunts is based largely on observations of the concerted activities of the mucosal capillaries. Knowledge of the operation of individual shunts is very meager. The effectiveness of the gastric and colic shunt systems in diverting blood from the mucosal capillaries is well known from observations on mucosal color changes. Such changes can be studied in the patient with a gastrostomy or a colostomy and can be seen moderately well through the sigmoidoscope. Observations on color changes during gastroscopy are not valid because of rapid variations in the incidence of the reflected light rays and in their source-to-mucosa distance.

The studies of Wolf and Wolff [71] on influences which can cause sudden blanching and reddening of the gastric mucosa, due to changes in mucosal blood content, are well known and require no elaboration. Although increase in mucosal redness is known to correlate well with increase in mucosal blood flow,[57] visual judgment of mucosal color is fraught with interpretational difficulties, and it has been necessary to find a more precise technique for measuring general mucosal capillary flow. Thermal gradientometry fills the need well. It measures blood flow in the capillaries of a specified mucosal area through the degree of cooling achieved when heat is applied to it. Studies by this technique confirm the observation that a sudden increase in gastric and duodenal mucosal capillary flow may result from emotional tension, anxiety, and resentment.[8,57] There is transitory acceleration of flow with each peristaltic wave, and appetizing stimuli produce an increase within 90 seconds. When gastric mucosal flow is measured during laparotomy, it is found that there is depression at the time of skin incision and a further drop when the stomach is handled.[11] This finding confirms well an observation made on the oxygen saturation of venous blood in the gastric veins during surgery [4,12]: Blood taken from a gastric vein immediately after the peritoneum was opened was found to have an oxygen saturation of 74%, i. e., its source was capillary. After the stomach had been handled just a few minutes, the saturation rose to 91%, suggesting that now the capillaries were being bypassed. No such change was found in blood drawn simultaneously from an arm vein. As Bentley [12] pointed out, this variability in gastric venous oxygen saturation is not surprising, because at operation it is common to find that soon after the peritoneum has been opened the serosal veins of the stomach change from dusky purple to bright red. The reverse effect does not obtain: altering the oxygen content of plasma perfusate does not influence shunt activity in freshly resected human stomachs.[68]

When the freshly resected stomach is studied at body temperature and is then suddenly cooled, it is found that the shunts are thrown open.[68] Similarly, reducing the pH of perfusion fluid from 7.6 and 7.8 to 7.4 encourages the shunts to open. This latter may prove to be a most significant point in making a correlation with the usual pattern of continuous gastric secretion in the duodenal ulcer patient if, as will be emphasized below, the gastroduodenal mucosa is harmed more by plethora than by ischemia. Secretion of acid by the stomach appears to be accompanied by liberation of equivalent amounts of alkali into the mucosal blood, and Walder [69] has suggested that if alkalinization of mucosal blood should exceed the capabilities of local buffering systems the arteriovenous shunts would respond by remaining closed. Consequently, the mucosa of the continuously secreting

stomach might be maintained in a continuously plethoric state.

It seems assured that the shunts are not able to maintain intermediate positions but are either fully open or fully closed. The contraction phase is a brief one.[24] The functional diameter of the shunts can satisfactorily be measured by noting the largest size glass spheres which when introduced into the arterial intake of the organ appear in the venous outflow. For the present discussion it is important to remember that the gastroduodenum has a system of shunts in the subserosa as well as at the base of the mucosa; therefore, it is possible although highly improbable that the functional diameters of the two systems differ—improbable because the functional diameters of the shunts in all organs throughout the body have been found to be about the same. For the gastroduodenum in both man and several species of experimental animal, measured in resected specimens and in situ, the maximum diameter has been reported at from 140μ to 160μ.[5,60,67] This proof of the function of shunts during life was provided by Sherman and Newman.[60]

Although it is clear from thermal gradientometer observations that the majority of gastroduodenal shunts act in concert, an important physiologic question revolves about the degree of paradoxical activity which normally exists among neighboring shunts. Obviously, this is a difficult matter to study. Little progress has been made in its solution. It is known from vivimicroscopic observations that in normal rats not all mucosal arteries are functioning at the same time.[6] Some remain patent for a while "and then suddenly collapse." Similarly, not all mucosal veins function at once. The submucosal shunts can be recognized in vivimicroscopic preparations, but only one can be satisfactorily studied at a time. They are often found to be closed, although they open quickly if the animal should pass into shock.[6] The rhythmic activity of a shunt is not simply a reflection of that of its arteriole; shunt and arteriole show different rhythmic rates and independent periods of closure.[21]

Study of the vessels of the gastroduodenum by injection with special masses in situ or after removal of the organ, with subsequent histopathologic or microradiographic examination, has taught a great deal about gastroduodenal vascular physiology. There have been objections to this approach because of the unnatural conditions which necessarily exist, especially that condition created by the pressure required for the injection. The mere fact that it permits comparison of the ability of the intramural vessels to receive injection masses during life, immediately after the extirpation of the organ, and long after death, however, makes it particularly useful for distinguishing pure anatomy from physiologic anatomy. It is the physiologic anatomy that is important, but this must be studied in connection with the dead anatomy if its physiologic aspect is to be recognized. The significance of vessel tone, shunt competence, etc. as they may vary from point to point along the stomach wall can be studied in no other way at the moment, although this is not to say that observations made on these points by this technique are necessarily valid. The consensus of experienced opinion is that the pressures attained during perfusion studies are not capable of influencing the state of the shunts,[68] but there may be some question in the case of injection studies.

Perhaps the most basic fact discovered through injection studies is that the injection mass fills the mucosal capillaries completely and evenly when cadaver stomachs are used, but there is almost no filling when fresh surgical specimens are used.[4,12] In other words, all of the shunts apparently open under the conditions which exist at operation and all are closed after death. When stomachs are resected under spinal anesthesia which reaches to T-1 or T-2, however, they show upon injection extensive capillary filling throughout the mucosa,[4,12] demonstrating again the potency of nervous

control over the shunts. Experimentally it has been reported that stimulation of the right vagus nerve decreases capillary filling in the pyloric mucosa of the stomach,[7] although this would not be the expected response and does not correlate well with the effect of acetylcholine on the shunt system, as discussed below.

Blood flow in the colon mucosa reacts to emotional and pharmaceutical stimuli as does that in the gastroduodenal mucosa,[28] judging by both color changes and thermal gradientometry study. It has, in addition, been shown that a cold stimulus applied to the body surface results in increased mucosal flow, with decrease when the skin stimulus is discontinued.[29] When the colon mucosa is infiltrated with procaine, the reflex neurologic influence over capillary flow disappears, although the ischemic effect of intravenous epinephrine is not blocked.

Pharmacology of Shunts

Pharmacologic influence over gastric mucosal capillary flow has been studied in some detail. Intramuscular histamine causes a significant and prolonged increase in capillary filling[47] and capillary flow within 15 minutes[6,57] after a transient decrease,[51] and there is a corresponding decrease in the flow of glass spheres through the shunts from the arterial to the venous side of the gastric circulation.[68] Amyl nitrite and glyceryl trinitrate (nitroglycerin) produce variable results. Vasopressin (Pitressin), which has played such a large part in experimental efforts at ulcer production, causes mucosal ischemia.[52] By injecting carbon into the aorta of vasopressin-treated rabbits, Crane[23] found that there was no capillary filling in those areas of the gastric mucosa which had responded to vasopressin by developing superficial necrosis, while histologically normal areas of the mucosa showed adequate filling. He seems to have proved that the ischemia developed before the ulcers appeared. Berg[13,14] emphasized the part that vascular innervation plays in governing mucosal damage after repeated injections of vasopressin, having found that sympathectomy afforded protection while vagotomy seemed to render the mucosa more vulnerable.

Epinephrine, ergotoxine, tetraethylammonium bromide, pilocarpine, and atropine cause depression of mucosal flow, with simultaneous increase in the utilization of the shunts.[5,42-45,68] The action of pilocarpine in this connection is complicated by its production of striking tonic contraction of the gastric muscular coats, with a constricting influence over the vessels which pierce them.[6,18] It should be noted that uncertainty regarding the quantitative effect of intramural muscular contraction on mucosal blood flow has interfered seriously with evaluation of pharmacologic influences over the shunts. For instance, Benjamin and colleagues[9] felt it necessary to ascribe the elimination by dicyclomine (Bentyl) hydrochloride of the usual mucosal temperature fall during hunger contractions entirely to the influence of dicyclomine over muscle tone.

Addition of small concentrations of acetylcholine to plasma used for perfusing freshly resected human stomachs causes marked reduction in the perfusion rate and increase in the total blood flow through the organ. That this is due to closing of the arteriovenous shunts is known because at the same time the passage of glass spheres through the gastric circulation is much reduced.[5] This is important because upon vagus nerve stimulation there is a distinct increase of acetylcholine in the venous blood which drains from the stomach and because, it is believed, in ulcer patients there is increased or perhaps constant vagus activity.[51] On the other hand, faradic stimulation of a sympathetic nerve accompanying the left gastric artery causes reduction in total flow through the stomach, with simultaneous increase in outflow of glass spheres, indicating that utilization of the shunts is much increased.[5,68]

Pathology of Shunts

Glomus tumors take their origin in arteriovenous shunts of the indirect type. Only a few cases have apparently been reported for the stomach.[1,25,36,40,41,62]

De Busscher[19] and Clara[20] have described inflammatory disease of the intermediate segment. Such a change might be expected to produce profound disturbances in the regional capillary circulation. The frequency of and cause for inflammatory disease localized to the shunt apparatus, in the absence of more generalized mucosal or submucosal inflammation, are not known. There may be infiltration of the intermediate segment with lymphocytes and neutrophils. The Schumacher cells may become displaced peripherally. This plus deposition of a fibrous sheath about the vessel may, in de Busscher's opinion, result in a permanently open shunt.

It is of immense importance that in patients with pernicious anemia, a disease regularly accompanied by chronic atrophic gastritis, the mucosal blood flow remains static, without variations secondary to peristalsis, etc.[19] Here the mucosal capillary net shrinks as the glands atrophy, and one supposes that if the shunts are rendered inactive or are actually destroyed it is due to the great hyperplasia of the muscularis mucosae, which is always part of the gastric pathology in pernicious anemia. The well-documented dictum that active benign duodenal ulcers never develop after pernicious anemia becomes established has a possible vascular explanation then.

The situation in cases of chronic atrophic gastritis not associated with pernicious anemia is not known, although a hint is to be found in the report of Kimbel and colleagues.[38] By the use of a swallowed microcounter, they found that the radioactivity picked up from the normal gastric mucosa after intravenous injection of P^{32} is related to the blood content of the mucosa and part of the submucosa. Oscillations in two phases were found, and these could be altered by various pharmacologic preparations, particularly histamine, in a series of patients being treated for polycythemia. In the one patient who had achlorhydria, however, the counts remained uninfluenced by histamine, suggesting that the mechanism controlling vascular dynamics had been lost as atrophy developed.

The mucosal vein beyond a shunt which lies above the muscularis mucosae is subjected to arterial pressure in a vulnerable anatomic location. It may at times be the source of severe gastric hemorrhage, according to Menegaux and colleagues.[46] They treated a patient who required gastrectomy for hemorrhage and, upon histopathologic examination of the specimen, believed they found evidence of this mechanism.

Comment

The reasons for believing that local tissue hypoxia ("ischemia" as originally stated should clearly have been broadened to "hypoxia") is the final change leading to ulcer formation have already been stated.[54] They have impressed many people, beginning perhaps with Virchow,[66] who in 1853 stated that ulcer must be considered a vascular trouble which acts through local ischemia, because gastric juice can attack only devitalized portions of the mucosa. Interest has been continued through the work and expressions of von Bergmann,[16] Hauser,[30] Wilkie,[70] Nedzel,[52] Herzog,[32] Berg,[14] Boles,[17] and many others. Back as far as 1913, Ophüls[53] was complaining, "The importance of local disturbances in circulation in the etiology of gastric and duodenal ulcer appears to be a well established fact with the majority of those who have made a close anatomical study of the condition. Still this view seems to be far from generally accepted."

The reason that discovery of the gastroduodenal shunt system has proved such a boon to thinking on the problem of the final common pathway[61] in ulcer genesis is that here one finds an explanation for local hypoxia and tissue necrosis which has a

physiologic basis—an explanation which does not depend on an already existing pathologic process in the gastroduodenal wall. It now becomes possible to satisfy one of the important criteria for any satisfactory theory of ulcer genesis, that the mechanism must permit the crater to be the result of an abnormal functional activity. The crater is, after all, merely a local manifestation of a systemic psychovisceral process. In observing the great incidence of ulcer and the notable propensity of the lesion to repeat over and over the cycle of breakdown and healing, one becomes convinced that the final common pathway must be a physiologic process gone wrong. Postulation of a hypoxia mechanism which depends on actual vascular pathology will not do, if one is to place proper emphasis on such common characteristics of the ulcer patient as his unique emotional pattern, his general neurovascular hyperirritability, his gastrointestinal hyperactivity, and the secretory peculiarities of his stomach. Prior to knowledge of the arteriovenous shunts, those who studied the problem had to concentrate on such possible mechanisms as embolization and intramural obliterative endarteritis, not being able to make much of a case for them but having no better possibilities to work with. It is not possible for such processes to explain the natural behavior of the ulcer. Parenthetically, it is important to note that this same mechanism of physiologically induced mucosal hypoxia, operating through arteriovenous shunt activity, may well be proved eventually to be the explanation for other more diffuse diseases of the gastrointestinal mucosa, as mentioned at the outset.

Little has been said here about the experimental production of ulcers, because to date no amount of effort has succeeded in the creation of anything that can be compared in a critical fashion with the chronic ulcer of the human gastroduodenum. It was discovered long ago that producing ulcers at will in experimental animals poses no problem. Ulcers have been created by a great many workers using many techniques. The trouble has been that all such ulcers are acute—they either progress rapidly or, if the artificial stimulus is removed, they heal quickly. The problem of producing self-sustaining ulcers has not been solved. In order to learn the factors which are active in the creation of ulcers, it is helpful, of course, to study conditions which exist at the time of inception; nevertheless, to answer even the more fundamental questions about etiology it is more profitable to keep the focus largely on the chronic ulcer—including its inception, of course, if that becomes possible—rather than concentrating on the much more easily studied acute artificially produced ulcer. For instance, as Aron and Sabassier [3] have pointed out, such lesions as those observed in the Shay rat are too unnatural to render their study worth while. Going directly to the ulcer patient and making retrospective observations on etiology have been more productive to date, if only because this approach has permitted the setting up of criteria, such as the recurrence matter, which must be met if an explanation for ulcer is to be satisfactory.

Under the hypoxic theory, it is assumed that the area in which the ulcer will form is maintained by shunt activity in a state of hypoxia often enough or continuously enough to depress its vitality or normal resistance below the point at which local noxious influences are able secondarily to injure it. Then the local state of hypoxia must be maintained at such a level that spontaneous healing cannot immediately proceed.

As to the mechanism of the initiating hypoxia itself, it must be emphasized that the mucosa may be rendered just as surely hypoxic under the conditions of capillary congestion or plethora as under those of ischemia. Although most authors who have discussed vascular factors in ulcer genesis have automatically assumed ischemia to be the responsible process,[48,54] it may fairly be asked whether a permanently closed shunt might not be more injurious to mucosal

health than a permanently open one. Both ischemia and the physiologic paradox of hypoxia through plethora are able to depress mucosal vitality to the point of necrosis, but it is probable that the latter is the usual explanation, for two reasons. First, all workers who have had the opportunity to study gastric mucosa through a gastrostomy have observed erosions to develop only as a sequel to mucosal engorgement. The same phenomenon can occasionally be proved at gastroscopic examination, and in certain clinical situations, such as the acute ulcerations which may result from prolonged shock, mucosal destruction is known to begin with a period of mucosal stasis and hyperemia.[59] These are, to be sure, quickly healing lesions which cannot be considered the same disease as chronic ulcer, but it proves that under these circumstances, at least, physiologically attained plethora is more injurious to the mucosa than physiologically attained ischemia. In the case of the well-established ulcer, there is histopathologic suggestion that engorgement with focal hemorrhage continues to act for some time in the periulcerous region.[2,37] Second, as has been pointed out above, the action of the pharmacologic preparations commonly used to produce experimental acute ulcers, other than vasopressin, is to cause shunt closure. The same is true for vagus activity. Under experimental circumstances vagus stimulation interrupts arteriovenous shunting, and vagotomy, so effective in the clinical management of ulcer, not only decreases mucosal blood content but also aggravates vasopressin ulceration, the only type of experimental ulcer which is clearly due to mucosal ischemia.

The shunts, as pointed out above, are under the control of both nervous and humoral influences. Neurologic vasomotor control of the gastroduodenum, mediated through the vagus nerves, is generally believed to arise in the hypothalamus, with higher connections to scattered areas throughout the anterior half of the cortex. The responsible humoral mechanism appears to be very complicated, even in its generalities, but seems to involve both the pituitary-adrenal axis and the intrinsic upper gastrointestinal hormones. There can be little disagreement that in the ulcer patient there is overt evidence of excessive physiologic activity along both these mediating pathways, apart from the vascular repercussions. Lack of appreciation of the extent of this activity can be blamed on the almost exclusive interest of past decades in its small secretory facet.

It is necessary to assume, of course, that the physiologic excess which leads to mucosal hypoxia affects different people in different ways—that there is at least a fair amount of individual variation in susceptibility to crater formation under similar conditions of hypoxia. In addition to the simple fact that throughout all of medicine individual variation in susceptibility to noxious circumstances is a prominent feature of the biology of disease, there is the interesting clinical observation that a portion of patients with the other clinical evidences of ulcer disease do not develop a crater.

With the hypoxia theory, as with all theories of ulcer genesis, the most difficult pathologic feature to explain is that of the circumscription and relative smallness of the resulting lesion. The problem of accounting for the usual localizations—the preponderance of bulbar over gastric ulcers, the relative rarity of greater-curvature gastric ulcers as compared with lesser-curvature ulcers, etc.—is almost as difficult. The old theory, once very popular, that stomach acid is concerned with ulcer genesis found these features impossible to explain. The hypoxia theory does not fare much better, but as yet there has been little thinking on the matter. The stimulus for doing so—for being impressed with the intramural, rather than the intraluminal, site of ulcerogenic activity—comes from both experimental and clinical observations. Such studies as those of Jávor and Varró[35] are impressive: In cinchophen-treated dogs which are actively developing acute gastric ulcers, the sites from which deep mucosal biopsy specimens

are taken heal spontaneously and quickly. Similarly, it is a regular observation in patients with either chronic duodenal or chronic gastric ulcer that the sites from which vacuum-tube mucosal biopsies (which reach into the submucosa) are taken heal completely in about two days, as judged gastroscopically, in spite of continued activity on the part of the ulcer.

The concerted happenings in the shunt system of the gastroduodenum as a whole are obviously insufficient to account for the generation of a focal lesion. Alternating generalized mucosal ischemia and plethora are, as pointed out above, a normal reaction to the stresses of normal living, and if a focal lesion is to develop a focal area of excess hypoxia or unusual susceptibility to normally occurring physiologic hypoxia must be postulated. In order to determine how excess focal hypoxia might come about, it is necessary that means be found for studying incoordinate activities among the shunts, to discover, perhaps, why one or a couple of the shunts should respond with inordinate sensitivity to the influences which cause them to close.

The matter of secondary obliterative disease of the arterial vessels which lie in the immediate vicinity of long-established ulcers deserves comment as a probable factor contributing to the chronicity of the lesion in some cases. This is not to be confused with etiology, for anatomic study of chronic ulcers reveals conditions which are much more likely to be effect than cause. This is known because in the case of new ulcers injection studies regularly show a striking increase in submucosal vascularity about and extending a little beyond the ulcer base, while in the case of chronic ulcers there is an ischemic zone about the sides and base of the lesion. The width of the zone correlates well with the amount of fibrosis beneath the crater. It is not so much that the regional arteries have become plugged as it is that the normal tissues have been replaced by relatively hypovascular connective tissue. The arterioarterial anastomotic net throughout the gastroduodenal wall is so tremendous that there would have to be almost total obliteration of the arterial supply before ischemia could result, and, as already discussed in some detail,[54] generalized gangrene rather than circumscribed ulcer would necessarily follow.

In thinking about the cycle of ulcer healing and recurrence, particularly the phenomenon which arranges for an ulcer to recur in the same spot occupied by the original lesion, it is important to note that the vascularity of the mucosa around an ulcer behaves very differently from the vascularity of the underlying periulcerous tissue. Thus, although a chronic ulcer is set in tissue which is notably hypovascular, the mucosa at the crater's edge is hypervascular. The criterion of ulcer healing is epithelization—a purely surface healing. It is reasonable to assume, after noting how quickly both chronic benign and cancerous ulcers sometimes become epithelized, that the mucosa can extend to cover large areas without much vascular help from the underlying diseased tissue. It is not known whether new mucosa over an old scar has its normal complement of shunts or not. At any rate, if new mucosa can form over a relatively bloodless ulcer scar, the fact of the local deep ischemia cannot very well be blamed for later break-down of the mucosa to form a new ulcer. Perhaps ischemia of the periulcerous zone explains why some chronic ulcers do not heal well, but there is no explanation here in the deep tissues for recurrence of the crater.

Some of the clinical behavioral features of ulcer fit in well with the vascular concept of etiology, and some do not. One of the most difficult matters to explain by the proposed theory is the development of the anastomotic ulcer, plus the effectiveness of the technical tricks of surgery (short afferent loop, etc.) which are known to discourage this form of ulcer. Pathologically this lesion seems very similar to the classical Cruveilhier ulcer. Although it is possible that it represents a different disease,[39] the

difficulty of visualizing a mechanism whereby the local shunt apparatus might be disturbed as a result of gastroenterostomy constitutes probably the main weakness of the theory. On the other hand, the effectiveness of the operative procedures as treatment for ulcer is easily understood. The main physiologic responsibility of the vagus nerves is vascular, not secretory, control of the gastroduodenum and small bowel, and vagotomy effects major alteration in shunt activity. It is proposed that gastrectomy is effective as treatment for duodenal ulcer at least partly because of the vagotomy it accomplishes.

Summary

The anatomy, physiology, pharmacology, and pathology of the gastroduodenal arteriovenous shunt system are reviewed as a preface for a discussion of hypoxia as the final common pathway in gastroduodenal ulcer genesis. Vascular theories of ulcer etiology are very old, but until the native arteriovenous shunts were discovered no reasonable mechanism could be postulated which would meet the most basic of the criteria for a proper etiologic explanation, that the crater must form as a result of a physiologic, not pathologic, excess or deficiency. It is proposed that the shunt mechanism, probably through induction of mucosal plethora rather than ischemia, supplies a reasonable explanation for hypoxia depression of mucosal vitality, the first step in crater formation.

2nd General Hospital, APO 180, New York.

REFERENCES

1. Allen, R. A., and Dahlin, D. C.: Glomus Tumor of the Stomach: Report of 2 Cases, Proc. Staff Meet. Mayo Clin. 29:429, 1954.

2. Amarante Júnior: Quelques aspects de la vascularisation de l'estomac ulcéré, Arch. mal. app. digest. 44:1258, 1955.

3. Aron, E., and Sabassier, H.: Recherches sur les résultats expérimentaux récents concernant la pathogénie vasculaire de l'ulcère, Arch. mal. app. digest. 43:1171, 1954.

4. Barclay, A. E., and Bentley, F. H.: The Vascularisation of the Human Stomach: A Preliminary Note on the Shunting Effect of Trauma, Gastroenterology 12:177,1949; Brit. J. Radiol. 22: 62, 1949.

5. Barlow, T. E.; Bentley, F. H., and Walder, D. N.: Arteries, Veins, and Arteriovenous Anastomoses in the Human Stomach, Surg. Gynec. & Obst. 93:657, 1951.

6. Basu Mallik, K. C.: An Experimental Study of the Pathogenesis of Gastric Ulcers Produced by Pilocarpine, J. Path. & Bact. 70:315, 1955.

7. Benjamin, H. B.: The Neurovascular Mechanism of the Mucous Membrane of the Stomach, Surg. Gynec. & Obst. 93: 672, 1951.

8. Benjamin, H. B.; Wagner, M., and Zeit, W.: Intragastric Temperature: Its Variations in Gastric Ulcers, Surg. Gynec. & Obst. 97:19, 1953.

9. Benjamin, H. B.; Wagner, M., and Zeit, W.: Bentyl Hydrochloride Effect on Intragastric Temperature—Normal Subjects, Am. J. Gastroenterol, 22:387, 1954.

10. Benjamin, H. B.; Wagner, M.; Zeit, W.; Pisciotta, A. V., and Ausman, R. K.: Intragastric Temperatures in the Achlorhydric Patient, Surg. Gynec. & Obst. 100:566, 1955.

11. Benjamin, H. B.; Wagner, M.; Zeit, W., and Ausman, R.: Thermogenesis During Surgical Anesthesia, Rev. canad. biol. 15:95, 1956.

12. Bentley, H. F.: An Arteriovenous Shunt in the Stomach Wall, Gastroenterologia 75:31, 1949.

13. Berg, M.: Experimental Studies on the Production of Peptic Ulcers by Vasomotor Alterations (Pitressin Episodes), Am. J. Digest. Dis. 7:78, 1940.

14. Berg, M.: Experimental Peptic Ulcerations by Vasomotor Episodes (Pitressin Episodes) and Autonomic Disturbances, Arch. Path. 33:636, 1942.

15. Berg, B. N.: Vascular Changes in the Mucosa in Experimental Nutritional Gastritis, Gastroenterology 7:340, 1946.

16. von Bergmann, G.: Ulcus duodeni und vegetatives Nervensystem, Berl. klin. Wchnschr. 50:2374, 1913.

17. Boles, R. S.; Riggs, H. E., and Griffiths, J. O.: The Role of the Circulation in the Production of Peptic Ulcer, Am. J. Digest. Dis. 6:632, 1939.

18. de Busscher, G.: Le Rôle joué par les couches musculaires dans la distribution du sang dans la paroi gastrique, Acta gastro-enterol. belg. 9:545, 1946.

19. de Busscher, G.: Les anastomoses artério-veineuses de l'estomac, Acta Neerl. morphol. norm. et path. 6:87, 1948.

20. Clara, M.: Die arterio-venösen Anastomosen: Anatomie, Biologie und Pathologie, Ed. 2, Wein, Springer-Verlag, 1956, p. 315.

21. Clark, E. R.: Arterio-Venous Anastomoses, Physiol. Rev. 18:229, 1938.

22. Conti, G., and Passarelli, L.: Contributo alla conoscenza dell'esofago umano, Arch. chir. torace 8:269, 1951.

23. Crane, W. A. J.: Histological and Arteriographic Studies on Pitressin Lesions of the Rabbit's Stomach, J. Path. & Bact. 67:379, 1954.

24. Curri, S. B., and Tischendorf, F.: Richerche sperimentali sull'istofisiologia e istopatologia delle anastomosi arterovenose: Asservazioni in vivo sul padiglione dell'orecchio del coniglio, Riv. anat. pat. e onc. 10:741, 1955.

25. Demin, V. N.: Glomus Tumor of the Stomach, Vopr. onkol. 1:113, 1955 (original not seen).

26. Disse: Über die Blutgefässe der menschlichen Magenschleimhaut, besonders über die Arterien derselben, Arch. mikr. Anat. 63:512, 1904.

27. Djørup, F.: Untersuchungen über die feinere topographische Verteilung der Arterien in den verschiedenen Schichten des menschlichen Magens, Ztschr. ges. Anat. 64:279, 1922.

28. Grace, W. J.; Wolf, S., and Wolff, H. G.: The Human Colon: An Experimental Study Based on Direct Observation of 4 Fistulous Subjects, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1951, p. 229.

29. Grayson, J.: Observations on Blood Flow in Human Intestine, Brit. M. J. 2:1465, 1950.

30. Hauser, G.: Die peptischen Schädigungen des Magens, des Duodenums, und der Speiseröhre und das peptische postoperative Jejunalgeschwür, in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag. 1926, Vol. 4, Pt. 1, pp. 339-811.

31. Herzog, W.: Zur Gefässhistologie des Magens und Zwölffingerdarmes beim Ulcus ventriculi und duodeni, Beitr. klin. Chir. 184:74, 1952.

32. Herzog, W.: Sur la Pathogénie vasculaire de l'ulcère gastro-duodénal, Arch. mal. app. digest. 42:1240, 1953.

33. Herzog, W.: Gefässveränderungen beim Ulcus ventriculi und duodeni, Beitr. klin. Chir. 188:236, 1954.

34. Hofmann, L., and Nather, K.: Zur Anatomie der Magenarterien: Ein Beitrag zur Aetiologie des chronischen Magengeschwüres und seiner chirurgischen Behandlung, Arch. klin. Chir. 115:650, 1921.

35. Jávor, T., and Varró, V.: Experimental Observations During the Development of Cinchophen Ulcer in Dogs, Gastroenterology 32: 119, 1957.

36. Kay, S.; Callahan, W. P., Jr.; Murray, M. R.; Randall, H. T., and Stout, A. P.: Glomus Tumors of the Stomach, Cancer 4:726, 1951.

37. Khalil, H. A.: A Histopathological Study of the Minute Vasculature of the Peptic Gastric Ulcer, J. Egyptian M. A. 39:57, 1956.

38. Kimbel, K. H.; Kinzlmeier, H., and Henning, N.: Untersuchungen zur Magendurchblutung: I. Versuche mit radioaktivem Phosphor, Gastroenterologia 82:317, 1954.

39. Konjetzny, G. E.: Die Geschwürsbildung in Magen, Duodenum und Jejunum: Entstehungsbedingungen und Entwicklungsgang, Stuttgart, Ferdinand Enke, 1947, p. 213.

40. Kostina, L. I.: Glomangioblastoma zheludka, Tr. Akad. med. nauk SSSR 21:16, 1952 (original not seen).

41. Mannix, A. J., Jr.; Schraft, W. C.; Reed, W. P., and Adie, G. C.: Glomus Tumor of the Stomach: Case Report, Surgery 37:473, 1955.

42. Masuda, H.; Ohara, M., and Katsura, S.: Studies on the Temperature of the Gastrointestinal Tract: Response of Intragastric Temperature to Various Drugs, Tohoku J. Exper. Med. 57:129 and 137, 1953.

43. Masuda, H.: Studies on the Temperature of the Gastrointestinal Tract: Response of Intragastric Temperature to Histamine, Tohoku J. Exper. Med. 58:39, 1953.

44. Masuda, H.; Ohara, M., and Katsura, S.: Studies on the Temperature of the Gastrointestinal Tract: Influence of Cold Bathing on Intragastric Temperature, Tohoku J. Exper. Med. 58:49, 1953.

45. Masuda, H.; Ohara, M., and Katsura, S.: Studies on the Temperature of the Gastrointestinal Tract: Relation of Intragastric Temperature to Gastric Secretion, Tohoku J. Exper. Med. 58:57, 1953.

46. Menegaux, G.; Gouygou, C.; Courtois-Suffit, M., and Détrie, P.: Hématémèses par dysfonctionnement des anastomoses artério-veineuses de la paroi gastrique, Presse méd. 61: 1328, 1953.

47. Miller, E. B., and Haszczyc, V. A.: Gastric Mucosal Capillaries in the Human, Arch. Surg. 73:465, 1956.

48. Mogena, H. G.: A Propos du facteur vasculaire de l'ulcère, Arch. mal. app. digest. 42: 1221, 1953.

49. Morris, W. R.: A Note on the Occurrence of an Arterio-Venous Anastomosis in the Human Oesophagus, New Zealand M. J. 54:690, 1955.

50. Moyson, F., and de Scoville, A.: Diagnostic et traitement des hémorragies digestives aiguës, Acta chir. belg., Supp. 1, p. 3, 1955.

51. Necheles, H.: The Phenomenon of Peptic Ulcer, Am. J. Digest. Dis. 16:237, 1949.

52. Nedzel, A. J.: Experimental Gastric Ulcer (Pitressin Fusodes), Arch. Path. 26:988, 1938.

53. Ophüls, W.: The Relation of Gastric and Duodenal Ulcer to Vascular Lesions, Arch. Int. Med. 11:469, 1913.

54. Palmer, E. D., and Buchanan, D. P.: On the Ischemic Basis of "Peptic" Ulcer: I. Historical Definition of Present Status, Ann. Int. Med. 38: 1187, 1953.

55. Pompeiano, O.: Anastomosi arterio-venose ed altri dispositivi vascolari regolatori del circolo nel duodeno, Arch. ital. anat. e istol. pat. 23:225, 1950.

56. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg. Gynec. & Obst. 30:374, 1920.

57. Richards, C. H.; Wolf, S., and Wolff, H. G.: The Measurement and Recording of Gastrointestinal Blood Flow in Man by Means of a Thermal Gradientometer, J. Clin. Invest. 21:551, 1942.

58. Schumacher, S.: Über das Glomus coccygicum des Menschen und die Glomeruli caudales der Säugetiere, Arch. mikr. Anat. 71:58, 1907.

59. Schumacher, S.: Über die Bedeutung der arteriovenösen Anastomosen und der epithelioden Muskelzellen (Quellzellen), Ztschr. mikr.-anat. Forsch. 43:107, 1938.

60. Sherman, J. L., Jr., and Newman, S.: Functioning Arteriovenous Anastomoses in the Stomach and Duodenum, Am. J. Physiol. 179:279, 1954.

61. Sherman, J. L., Jr.: The Final Common Pathway in Ulcer Genesis, U. S. Armed Forces M. J. 7:1001, 1956.

62. Spängler, H.: Über ein Angioneuromyom (Glomustumor) des Magens und andere neurogene Geschwülste des Magen-Darmtraktes, Chirurg 24: 181, 1953.

63. Spanner, R.: Die arteriovenösen Anastomosen, Fortschr. diag. Therap. 1:1, 1950.

64. Staubesand, J.: Über die Entstehung "intravasaler Apparate," Verhandl. anat. Gesellsch. 52: 240, 1954.

65. Staubesand, J.: Zur Problematik der sogenannten Polsterarterien in der Magenwand, Beitr. klin. Chir. 190:367, 1955.

66. Virchow, R.: Historisches, Kritisches und Positives zur Lehre der Unterleibsaffektionen, Arch. path. Anat. 5:632, 1853.

67. Walder, D. N.: Arteriovenous Anastomosis in the Stomach Wall: Preliminary Communication, Lancet 1:162, 1950.

68. Walder, D. N.: Arteriovenous Anastomoses of the Human Stomach, Clin. Sc. 11:59, 1952.

69. Walder, D. N.: The Vascularisation of the Stomach in Relation to the Aetiology of Peptic Ulcer, Gastroenterologia 81:66, 1954.

70. Wilkie, D. P. D.: The Blood Supply of the Duodenum, with Special Reference to the Supraduodenal Artery, Surg. Gynec. & Obst. 13:399, 1911.

71. Wolf, S., and Wolff, H. G.: Human Gastric Function: An Experimental Study of a Man and His Stomach, New York, Oxford University Press, 1947, p. 251.

The Clinical Significance of Serum Cyanocobalamin (Vitamin B_{12}) in Liver Disease

M. RACHMILEWITZ, M.D.; Y. STEIN, M.D.; J. ARONOVITCH, M.Sc., and N. GROSSOWICZ, Ph.D., Jerusalem

Concentrations of cyanocobalamin (vitamin B_{12}) in serum have been found to be elevated in acute [1-4] and chronic [2,5,6] liver disease associated with hepatocellular damage. In acute viral hepatitis the rise in serum cyanocobalamin was most pronounced in the first two weeks of the disease, when bilirubinemia is marked and the liver-function tests indicative of hepatocellular damage are positive. In cirrhosis of the liver elevated cyanocobalamin values were found when clinical and laboratory signs of active hepatitis were present. In extrahepatic obstructive jaundice the serum cyanocobalamin level was found to be normal.[1,3]

These studies were extended to a larger group of patients. The serum cyanocobalamin values were correlated with the common liver-function tests and particularly with the degree and duration of bilirubinemia. It appeared from these studies that the estimation of serum cyanocobalamin may serve as an early and sensitive test for differentiating the various types of jaundice. The clinical significance of this test will be discussed in this communication.

Patients

There were 37 patients with viral hepatitis, comprising a heterogenous group of adults, mostly new immigrants to Israel, with poor nutritional backgrounds. In some of the patients the epidemiological and clinical data indicated homologous serum jaundice. One patient with acute yellow atrophy of the liver due to phosphorus poisoning was also studied. There were 14 patients with portal cirrhosis, including 5 who showed clinical and laboratory signs of active hepatitis. Six patients were in the advanced stage of portal cirrhosis in decompensation. The remaining three patients had compensated portal cirrhosis.

There were six patients with biliary cirrhosis, in five of whom the diagnosis was confirmed by laparotomy, liver biopsy, or postmortem examination. One of these patients had primary biliary cirrhosis, confirmed by liver biopsy.

A group of 12 patients with extrahepatic obstruction due to choledocholithiasis or carcinoma of the head of the pancreas was also studied. The diagnosis in these patients was established on clinical grounds and verified by laparotomy or postmortem examination. Finally, two patients with chlorpromazine jaundice were examined. The clinical and laboratory manifestations in these patients were characteristic of obstructive jaundice without hepatocellular damage. In one of these two patients liver biopsy verified the absence of hepatocellular damage.

Methods

The serum cyanocobalamin was estimated by the modified Escherichia coli assay.[7] The total serum cyanocobalamin was determined after liberation of the vitamin from the serum proteins by acid precipitation.[8] Since E. coli responds to methionine as well as to cyanocobalamin, control assays were run on serum extracts after alkaline hydrolysis at pH 12 to destroy the vitamin. Practically no growth-promoting activity was found after this treatment. In healthy persons the serum cyanocobalamin values ranged from 200$\mu\mu$g. to 500$\mu\mu$g. per milliliter.

Results

Acute Hepatitis.—The majority of the patients with acute viral hepatitis were admitted a week or more after the onset of the jaundice; at this time usually the highest

Submitted for publication Oct. 3, 1957.

This work was supported by grants from the Hematology Research Foundation, Chicago, and from the Hadassah Medical Organization, Jerusalem.

From the Department of Medicine "B," Hadassah-University Hospital, and Department of Bacteriology, Hebrew University-Hadassah Medical School.

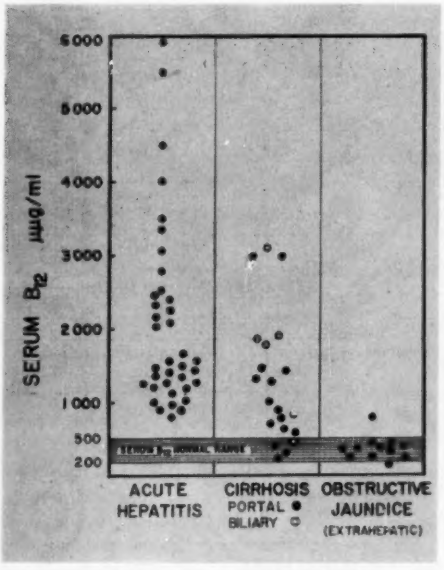


Fig. 1.—Serum cyanocobalamin in patients with hepatobiliary disease. Each dot represents the admission level determined in a single patient.

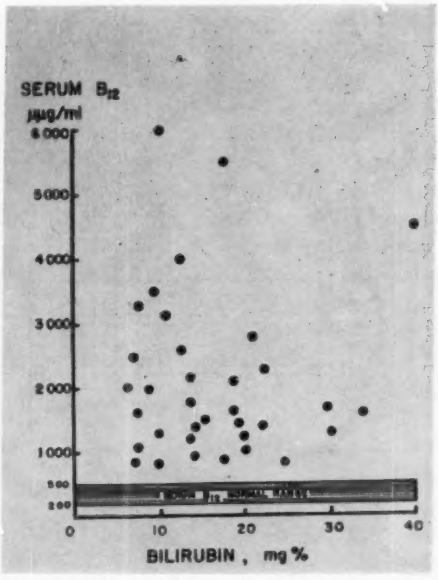
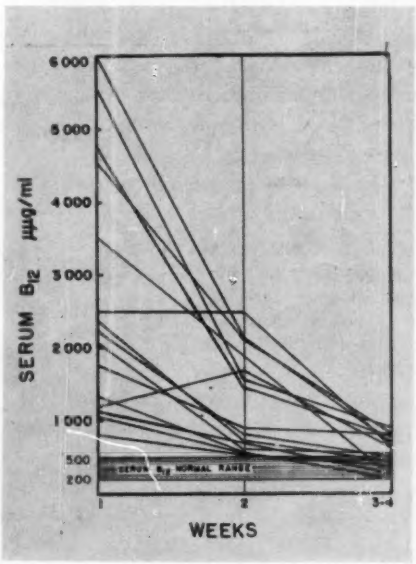


Fig. 2.—Admission values of serum cyanocobalamin and bilirubin in patients with acute viral hepatitis.

level of bilirubin in the serum was found. In all these patients the first serum cyanocobalamin level determined after admission was elevated but ranged widely from 700$\mu\mu$g. to 6000$\mu\mu$g. per milliliter (Fig. 1). There was no definite correlation between the high initial serum cyanocobalamin values and the degree of bilirubinemia (Fig. 2). Thus concentrations of cyanocobalamin ten- to twentyfold greater than normal were associated with moderately elevated serum bilirubin concentrations, while sometimes only moderate elevations of serum cyanocobalamin were found in patients with marked bilirubinemia. The latter patients had the cholangiolitic type of viral hepatitis.[9] They had markedly increased serum bilirubin, alkaline phosphatase, and total cholesterol, while the liver-function tests indicative of hepatocellular damage were either normal or only slightly altered.

During the course of viral hepatitis the serum cyanocobalamin concentrations fell progressively during the third or fourth week of the disease. The decrease was most rapid in patients with very high initial values (Fig. 3). Irrespective of the initial degree of bilirubinemia, the decrease in the serum cyanocobalamin level occurred concomitantly with the decrease in serum bilirubin

Fig. 3.—Weekly serum cyanocobalamin determinations in 15 patients with acute viral hepatitis.



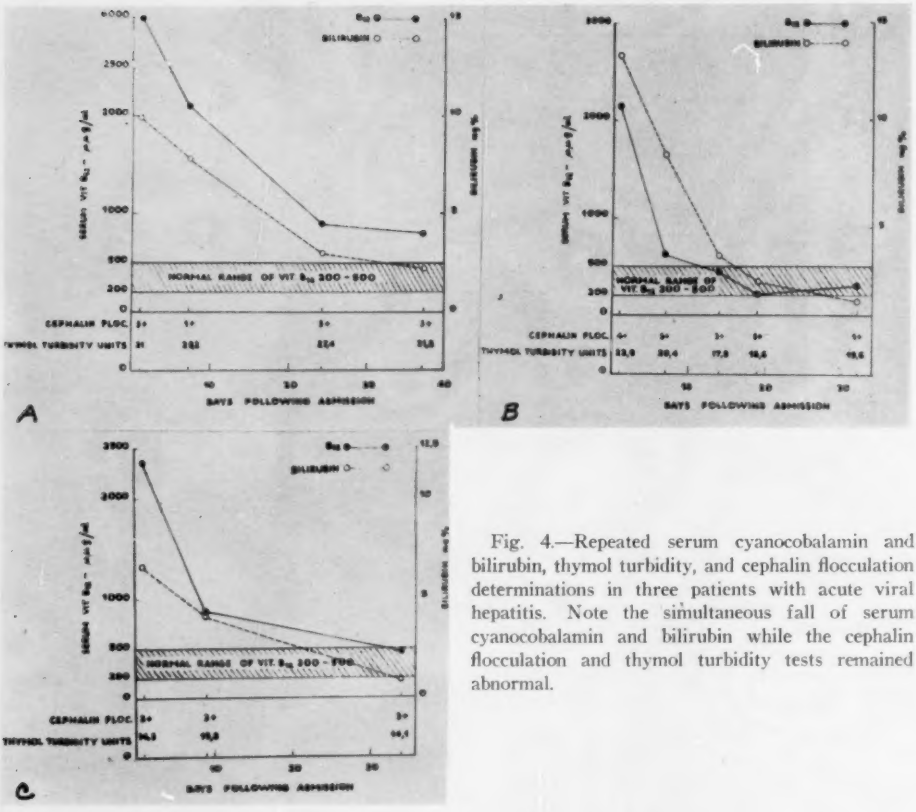


Fig. 4.—Repeated serum cyanocobalamin and bilirubin, thymol turbidity, and cephalin flocculation determinations in three patients with acute viral hepatitis. Note the simultaneous fall of serum cyanocobalamin and bilirubin while the cephalin flocculation and thymol turbidity tests remained abnormal.

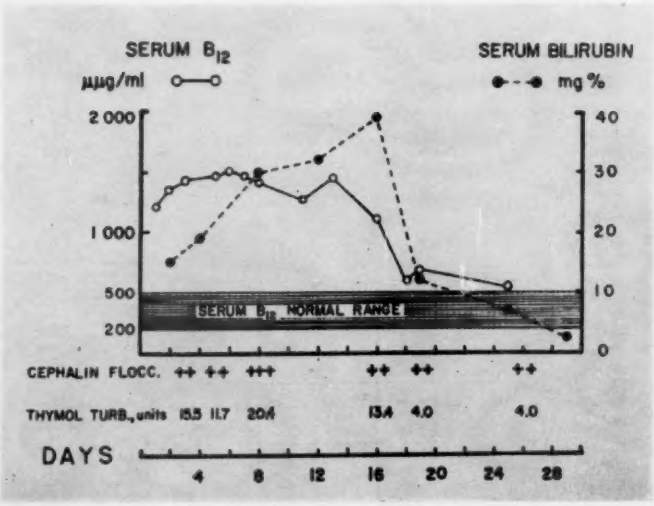


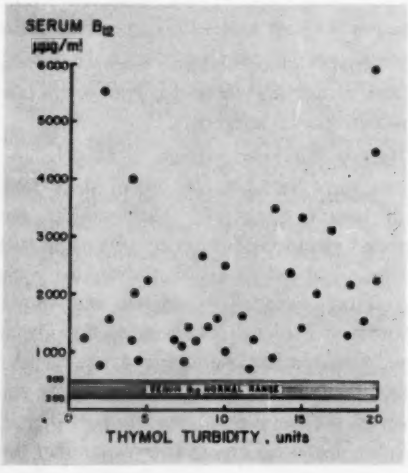
Fig. 5.—Serial serum cyanocobalamin and bilirubin, thymol turbidity, and cephalin flocculation in a case of acute viral hepatitis.

(Figs. 4, 5, and 7). The lack of correlation between concentrations of cyanocobalamin and bilirubin during the height of the disease, with simultaneous subsidence of both, was seen in a boy aged 13 in whom 14 cyanocobalamin determinations were performed during 24 days of persistent jaundice. The serum bilirubin increased markedly during a fortnight from 14.3 to 38.4 mg. per 100 cc., while the serum cyanocobalamin concentrations remained elevated at the same level. The serum bilirubin as well as the serum cyanocobalamin value then began to fall (Fig. 5).

The flocculation tests indicated hepatocellular damage in most of these patients. Some correlation was found between the serum cyanocobalamin level and the degree of thymol turbidity (Fig. 6). However, when jaundice had subsided and the cyanocobalamin levels had fallen to normal or were only moderately elevated, the flocculation tests were sometimes still abnormal (Fig. 4).

Among the patients with viral hepatitis the highest level of cyanocobalamin was found in two severely ill patients. The first was a woman, aged 57, who was admitted on Jan. 11, 1956, in the first week following the onset of jaundice. On admission she appeared severely ill, with marked anorexia and frequent vomiting. The first cyanocobalamin estimation, performed on Jan. 13, revealed 6000$\mu\mu$g. per milliliter, although the serum bilirubin was only 9.9 mg. per 100 cc. The cephalin flocculation was 3+, and thymol turbidity, 21 units. On Jan. 21, when the clinical condition improved considerably and the bilirubin value began to fall, the serum cyanocobalamin decreased to 2000$\mu\mu$g. per milliliter, whereas the thymol turbidity rose to 29 units. Two weeks later, when the bilirubinemia had fallen to 3 mg. per 100 cc., the serum cyanocobalamin was 900$\mu\mu$g. per milliliter (Fig. 4*A*).

Fig. 6.—Admission values of serum cyanocobalamin and thymol turbidity in patients with acute viral hepatitis.



The second patient was deeply jaundiced on admission. Two months before, the patient underwent subtotal gastrectomy for duodenal ulcer and received several blood transfusions. A few days before admission jaundice developed and progressed rapidly. The day following admission the patient went into hepatic coma, from which he recovered rapidly. The serum cyanocobalamin concentrations on admission and two days later, when the patient was in hepatic coma, were 4500$\mu\mu$g. and 3800$\mu\mu$g. per milliliter, respectively. With the rapid clinical improvement, the serum cyanocobalamin value fell further, reaching normal values four weeks later (Fig. 7). The 24-hour urinary excretion of cyanocobalamin determined during the precipitous fall in serum cyanocobalamin was very high, 14μg. Smaller amounts, 2.0μg. to 3.3μg., were excreted during the subsequent gradual decline of serum cyanocobalamin concentration.

An exceptionally high serum cyanocobalamin concentration (13,000$\mu\mu$g. per milliliter) was found in a fatal case of acute yellow atrophy due to phosphorus intoxication.

Cirrhosis of the Liver.—Portal Cirrhosis: Five patients with portal cirrhosis showed clinical and laboratory findings of active hepatitis manifested by jaundice and severely altered hepatocellular liver-function tests. All five patients had markedly ele-

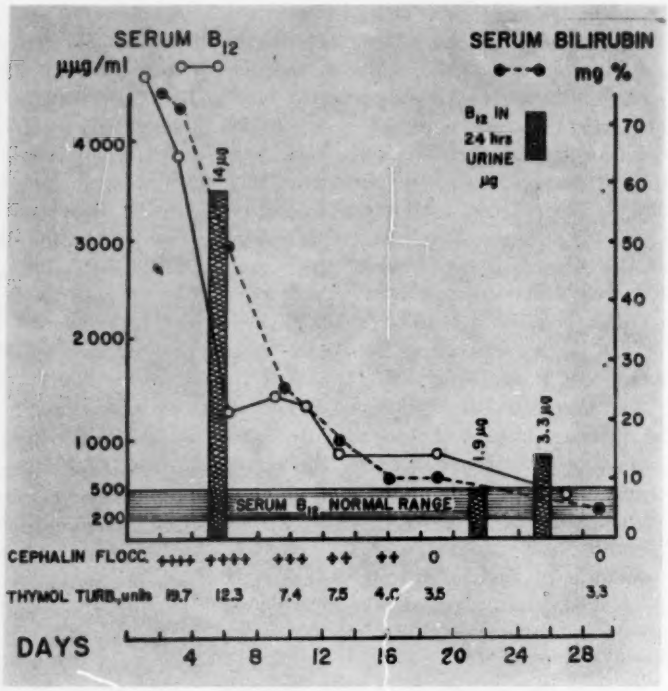


Fig. 7.—Serum cyanocobalamin and bilirubin, cephalin flocculation, thymol turbidity, and cyanocobalamin in 24-hour urine in a case of severe viral hepatitis.

vated cyanocobalamin values, ranging from 1000μμg. to 3500μμg. per milliliter (Fig. 1).

A case illustrative of persistent active hepatitis in portal cirrhosis was that of a 39-year-old man suffering from severe decompensated cirrhosis, manifested by generalized anasarca, persistent jaundice, marked hypoalbuminemia, and strongly positive flocculation tests. During the entire period of observation of over two months, signs of active hepatitis continued, and seven repeated determinations of cyanocobalamin in the serum showed consistently high values, ranging from 3000μμg. to 3500μμg. per milliliter.

An example of recurrent hepatitis in cirrhosis was represented by a 26-year-old woman in whom cirrhosis developed after viral hepatitis. At the time of observation, the patient was jaundiced for the third time in 12 years. The highest cyanocobalamin value (1450μμg. per milliliter) was found in the first week of jaundice and subsided gradually over a four-week period to normal levels (300μμg. per milliliter), with clinical recovery and decrease of bilirubinemia.

The six patients in advanced portal cirrhosis had clinical signs of portal hypertension but no evidence of active hepatitis and no jaundice at the time of examination. The cyanocobalamin values in these patients were lower than in the previous group and ranged between 900μμg. and 1250μμg. per milliliter.

Normal cyanocobalamin values were found in the remaining three patients with compensated portal cirrhosis.

Biliary Cirrhosis: High cyanocobalamin values were found in five out of six patients with biliary cirrhosis. The patients with elevated cyanocobalamin concentrations were in the advanced stage of the disease (Fig. 1). They were all jaundiced and showed laboratory evidence of hepatocellular damage. One patient suffering from primary biliary cirrhosis was not jaundiced and showed no histological evidence of hepatocellular damage. The cyanocobalamin values

in this patient on two examinations were within the normal range.

Obstructive Jaundice.—The jaundice due to extrahepatic obstruction by stones or carcinoma of the head of the pancreas varied in intensity and duration. In patients with jaundice due to bile-stone obstruction there was clinical evidence of ascending cholangitis. The cyanocobalamin values in this group varied from 160$\mu\mu$g. to 725$\mu\mu$g. per milliliter (Fig. 1). The slightly elevated serum cyanocobalamin (725$\mu\mu$g. per milliliter) was found in a patient with carcinoma of the head of the pancreas, six weeks after onset of jaundice.

In two patients with chlorpromazine jaundice, the clinical and laboratory manifestations were characteristic of obstructive jaundice without hepatocellular damage. In both cases the serum cyanocobalamin concentrations were normal.

Comment

The findings presented in this paper confirm our previous observations that hepatocellular damage is invariably associated with a high concentration of cyanocobalamin in the serum. This rise was found to be particularly striking in the early stage of viral hepatitis. In cirrhosis of the liver the cyanocobalamin concentration was always high when active hepatitis was present.

These observations suggested that hepatocellular damage in acute as well as in chronic liver disease results in the release of stored cyanocobalamin into the blood stream from disintegrating liver cells. Definite proof of this assumption was provided by experiments in dogs in which acute liver necrosis was produced by intragastric and intraportal CCl_4 administration. A conspicuous rise of serum cyanocobalamin was found in the first two hours after intraportal injection of CCl_4, by which time necrosis of an extensive part of the liver had developed.[10]

If liver necrosis is responsible for the rise of cyanocobalamin in the blood, then in liver disease without hepatocellular damage normal serum cyanocobalamin concentrations should be anticipated. This was indeed the case in diseases of the liver where the main pathology was limited to the cholangioles, such as chlorpromazine jaundice and primary biliary cirrhosis. These cases had the clinical and laboratory characteristics of obstructive jaundice, and liver biopsy performed in some showed no or slight evidence of hepatocellular injury.

In the early stages of jaundice due to obstruction of the extrahepatic bile ducts as well, there is no hepatocellular damage. Accordingly, the serum cyanocobalamin in these patients was found to be normal almost without exception. The serum cyanocobalamin determination may thus be of diagnostic value in differentiating hepatocellular from extrahepatic obstructive jaundice. In our experience, extending over three years, during which about 100 patients with hepatobiliary disease were studied, the serum cyanocobalamin determination served as a most useful and specific diagnostic test for the presence and degree of hepatocellular damage.

The reported observations also indicate the value of serum cyanocobalamin determinations in ascertaining the presence, degree, and duration of activity in chronic hepatitis. In patients with cirrhosis of the liver, high serum cyanocobalamin levels were always found when clinical and laboratory findings indicated active hepatitis. The increased cyanocobalamin levels persisted as long as the active process continued.

It has been shown that infiltration of liver parenchyma by tumor tissue may also lead to increased serum cyanocobalamin values due to the release of stored vitamin from damaged liver cells.[11] Hence, invasion of tumor into the liver in extrahepatic jaundice caused by malignancy may result in a rise of serum cyanocobalamin. This occurred in two patients with carcinoma, originating from the large extrahepatic bile ducts in one and from the head of the pancreas in the second (not included in this report), in whom extensive invasion of the tumor into the liver

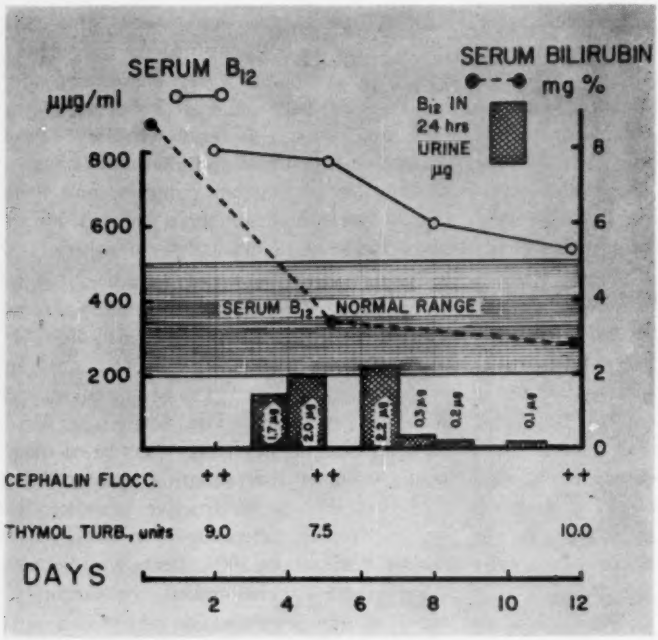


Fig. 8.—Serum cyanocobalamin and bilirubin, thymol turbidity, cephalin flocculation, and cyanocobalamin in 24-hour urine in a case of portal cirrhosis during the active phase of the disease.

was manifested by a high serum cyanocobalamin value.

The fall in serum cyanocobalamin level during the course of viral hepatitis may be explained by the cessation of additional hepatocellular damage and the excretion of cyanocobalamin in the urine. The determination of urinary excretion of cyanocobalamin in a few cases of acute hepatitis and in one case of active stage of portal cirrhosis revealed that the precipitous fall of serum cyanocobalamin was accompanied by increased excretion of cyanocobalamin in the urine (Figs. 7 and 8). This finding agrees with those of others,[3,4] who found increased amounts of cyanocobalamin in the urine of patients with acute hepatitis and Laennec's and postnecrotic cirrhosis.

The liberation of stored cyanocobalamin from the liver and its urinary excretion in large amounts during viral hepatitis and active hepatitis in cirrhosis results in loss of a vitamin which plays an important role in erythropoiesis and other biologic functions. Depletion of cyanocobalamin stores of the liver has been demonstrated in cirrhosis.[12] This depletion may well be responsible for the development of macrocytic anemia in some cases of cirrhosis. The development of cyanocobalamin deficiency in liver disease may thus be readily explained. The question of whether treatment with cyanocobalamin in liver disease is justified and beneficial cannot be answered at present with certainty. Contrary to findings in macrocytic anemias due to cyanocobalamin deficiency, the level of cyanocobalamin in the blood in liver disease does not reflect the concentration of the vitamin in the storage organ. However, low serum cyanocobalamin levels in the inactive stage of liver disease certainly indicate cyanocobalamin depletion.

As liver cells are a rich source of metals and various enzymes, substances other than cyanocobalamin may be released into the circulation from damaged cells. Of the metals, the best studied has been serum iron, which is known to be raised in acute hepatitis.[13] Wróblewski and LaDue[14] reported that the level of glutamic transaminase in the serum was elevated in acute and chronic liver disease and in experimentally produced

liver-cell damage by CCl_4. Other enzymes [15] have also been found in increased amounts in serum of patients with liver damage. In some cases included in this report cyanocobalamin and transaminase estimations were performed simultaneously in our laboratory.[18] The comparative studies showed that serum glutamic oxalacetic transaminase was slightly elevated in both extra- and intrahepatic biliary obstruction, confirming the observations of others,[14,16,17] whereas the cyanocobalamin values were normal in these conditions.

Summary

The serum cyanocobalamin (vitamin B_{12}) level is a very sensitive index of hepatocellular damage and is a valuable aid in differentiating hepatic from extrahepatic jaundice.

In acute viral hepatitis the serum cyanocobalamin level was considerably increased in the early icteric phase of the disease.

The highest serum cyanocobalamin value was found in acute yellow atrophy of the liver due to phosphorus intoxication.

In cirrhosis of the liver the serum cyanocobalamin was high when clinical and laboratory signs of active hepatitis were present.

In extrahepatic obstructive jaundice the serum cyanocobalamin levels were within the normal range.

The Hebrew University-Hadassah Medical School, P. O. Box 1172.

REFERENCES

1. Rachmilewitz, M.; Aronovitch, J., and Grossowicz, N.: Increased Serum B_{12} Concentrations in Liver Damage, Harefuah 49:267, 1955.

2. Rachmilewitz, M.; Aronovitch, J., and Grossowicz, N.: Serum Concentration of Vitamin B_{12} in Acute and Chronic Liver Disease, J. Lab. & Clin. Med. 48:339, 1956.

3. Kristensen, H. P. Ø.: B_{12}-vitaminhold i plasma ved akut hepatitis og occlusionsicterus: Foreløbig meddelelse, Nord. med. 55:85, 1956.

4. Jones, P. N.; Mills, E. H., and Capps, R. B.: The Effect of Liver Disease on Serum Vitamin B_{12} Concentrations, J. Lab. & Clin. Med. 49:910, 1957.

5. Lear, A. A.; Harris, J. W.; Castle, W. B., and Fleming, E. M.: The Serum Vitamin B_{12} Concentration in Pernicious Anemia, J. Lab. & Clin. Med. 44:715, 1954.

6. Jandl, J. H., and Lear, A. A.: The Metabolism of Folic Acid in Cirrhosis, Ann. Int. Med. 45:1027, 1956.

7. Grossowicz, N.; Aronovitch, J., and Rachmilewitz, M.: Determination of Vitamin B_{12} in Human Serum by a Mutant of Escherichia Coli, Proc. Soc. Exper. Biol. & Med. 87:513, 1954.

8. Spray, G. H.: An Improved Method for the Rapid Estimation of Vitamin B_{12} in Serum, Clin. Sc. 14: 661, 1955.

9. Eliakim, M., and Rachmilewitz, M.: Cholangiolitic Manifestations in Virus Hepatitis, Gastroenterology 31:369, 1956.

10. Stein, Y.; Stein, O.; Aronovitch, J.; Grossowicz, N., and Rachmilewitz, M.: Serum Vitamin B_{12} in Experimental Liver Injury, Bull. Res. Council Israel 6E:5, 1956.

11. Grossowicz, N.; Hochman, A.; Aronovitch, J.; Izak, G., and Rachmilewitz, M.: Malignant Growth in the Liver and Serum-Vitamin-B_{12} Levels, Lancet 1:1116, 1957.

12. Swendseid, M. E.; Hvolboll, E.; Schick, G., and Halsted, J. A.: The Vitamin B_{12} Content of Human Liver Tissue and Its Nutritional Significance: A Comparison Study of Various Age Groups, Blood 12:24, 1957.

13. Hemmeler, G.: Serumeisen bei Ikterus, Helvet. med. acta 6:678, 1939.

14. Wróblewski, F., and LaDue, J. S.: Serum Glutamic Oxalacetic Transaminase Activity as an Index of Liver Cell Injury: A Preliminary Report, Am. Int. Med. 43:345, 1955.

15. Bing, R. J.; Castellanos, A., and Siegel, A.: Diagnostic Value of Activity of Malic Dehydrogenase and Phosphohexose Isomerase: Preliminary Report of Findings in Patients with Myocardial Infarction and Liver Disease, J. A.M. A. 164:647, 1957.

16. Molander, D. W.; Sheppard, E., and Payne, M. A.: Serum Transaminase in Liver Disease, J. A. M. A. 163:1461, 1957.

17. Chinsky, M., and Sherry, S.: Serum Transaminase as a Diagnostic aid, A. M. A. Arch. Int. Med. 99:556, 1957.

18. Halpern, Y., and Weisskopf, H.: To be published.

The Electrocardiogram in Myocardial Infarction

Diagnostic Accuracy

MORRIS M. WEISS, M.D., and MORRIS M. WEISS Jr., Louisville

There are differences of opinion as to whether electrocardiograms can be normal in the presence of an acute myocardial infarction. Some authors claim that the records are never strictly normal.[1-3] Holzman [4] states that he has observed only 2 out of 100 cases of infarction with "negative tracings." In contrast, Prinzmetal et al.[5] claim that an acute myocardial infarction may fail to alter the electrocardiogram. The statement is based on their dog experiments,[6,7] which showed that diffuse lesions of the deeper layers of the myocardium, especially the subendocardium, did not produce abnormal tracings. They also observed two persons with pure subendocardial lesions which were diagnosed only after death. One patient died of carcinoma of the stomach, and the other, of pneumonia; both had essentially normal electrocardiograms.

This report is a study of the electrocardiograms of 304 cases of myocardial infarction as proven at autopsy. The autopsies were studied at five hospitals in this city. Table 1 gives the age and sex distribution of the cases. There were 209 males (69%) and 95 females (31%).

In every instance abnormal electrocardiograms were recorded. Table 2 lists the general classification of the abnormalities which were noted in the records. In 247 cases (81.5%) the abnormalities were those considered specific for an infarction. In 36 cases (11.5%) the abnormalities were nonspecific, which included complete A-V dissociation and ventricular tachycardia. The remainder of the cases, 21, or 7% of the total, showed left bundle-branch block.

TABLE 1.—*Analysis as to Age and Sex*

Age	Male	Female	Total
30–39	5	2	7
40–49	26	5	31
50–59	40	18	58
60–69	75	27	102
70–79	52	37	89
80–89	10	6	16
90+	1	—	1
	209	95	304

The results of our study are similar to those made by others. Feil, Cushing, and Hardesty [8] studied 34 cases of recent myocardial infarction in which necropsy was performed. All the electrocardiograms were abnormal in some way. All first single acute infarcts were readily diagnosed. Levine and Phillips [9] found that of 66 autopsied cases of myocardial infarction, all had abnormal electrocardiograms. McCain, Kline, and Gilson [10] studied the electrocardiograms of 182 subjects with myocardial infarction proven at autopsy. The records were taken some time after the occurrence of the infarction. A completely normal electrocardiogram was found in only two patients, but both had records made with only one chest lead. Myers, Klein, and Stofer [11] correlated the electrocardiogram with the autopsy diagnosis of 161 cases of myocardial infarction. All the electrocardiograms were abnormal. Rubin and Weiss [12] studied

TABLE 2.—*Electrocardiographic Findings*

Type	Cases, No.
Specific abnormalities	247
Nonspecific abnormalities	36
Left bundle-branch block	21

Submitted for publication Nov. 2, 1957.

Associate Professor of Medicine (Dr. M. M. Weiss) and Student Research Scholar M. M. Weiss Jr.), University of Louisville School of Medicine.

the electrocardiograms of 56 diabetic and 52 nondiabetic persons who had myocardial infarction proven at autopsy. In no instance were the electrocardiograms interpreted as normal. Zinn and Cosby [13] evaluated the diagnostic accuracy of the electrocardiogram in 679 autopsied cases of myocardial infarction. They concluded that repeated normal electrocardiograms suggest the absence of an infarct.

It is contended by some authors that various areas of the heart, when infarcted, may not produce abnormal ECG's. Holzman [4] states that "silent" ECG tracings may be obtained when infarcts involve the lateral wall, the middle layers of the ventricular wall, or parts of the septum. Levy and Hyman [14] list the areas of the heart in which the ECG diagnosis of an infarction may be missed: septum, superior portion of left ventricle adjacent to the A-V junction, and superior portion of lateral wall of left ventricle. Prinzmetal et al.[6] have attempted to prove that the subendocardium does not contribute to the genesis of the electrocardiogram. In contrast to the above statements, Dunn, Edwards, and Pruitt [15] claim that infarcts of the lateral wall of the left ventricle, particularly in the acute phases, are not electrocardiographically "silent." Scher et al.[16] in their dog experiments found that the endocardium was electrically active, and Guraieb and Rigdon [17] found abnormal electrocardiograms in all cases of endocardial fibroelastosis in adults whom they observed. Myers et al.[18] found that infarcts confined to the subendocardial part of the free wall of the left ventricle caused abnormal ECG's.

Lepeschkin [19] lists the causes for failure of the ECG to result in a characteristic pattern: registration of only one electrocardiogram, resulting in failure to recognize serial changes; presence of digitalis action; left bundle-branch block; presence of multiple infarcts which partly neutralize their respective patterns. Barnes [20] claimed that if the anterior apical and posterior basal portions of the left ventricle are simultaneously involved, the typical findings of the infarction may not be found, since these two regions have opposing effects on the ventricular complexes. In addition to these causes are mentioned bizarre patterns of intraventricular conduction disturbance and complete A-V block; combination of multiple old and new infarcts; pericarditis with or without an effusion.[2,8,20]

In this study, when the initial ECG was confusing, serial changes in the records were helpful in arriving at a diagnosis. This did not always apply to left bundle-branch block.

Summary

A study was made of 304 cases of myocardial infarction as proven at autopsy. In 247 cases (81.5%) the abnormalities were those considered specific for an infarction. In the remainder the abnormalities were nonspecific or were those of left bundle-branch block.

If serial records are obtained, a normal electrocardiogram is never recorded in a pathologically proven case of myocardial infarction.

Dr. J. D. Allen, Kentucky Baptist Hospital; Dr. M. Barnes, Norton Memorial Infirmary; Dr. S. Black, St. Joseph Infirmary; Dr. W. M. Christophersen, Louisville General Hospital; Dr. A. J. Miller, Jewish Hospital, and Dr. H. Gordon, Saints Mary and Elizabeth Hospital, cooperated in this study.

614 Brown Building (2).

REFERENCES

1. Evans, W.: The Distinctive Electrocardiogram of Coronary Arteriospasm, Brit. Heart J. 17:15-27 (Jan.) 1955.

2. Goldberger, E.: Heart Disease, Ed. 2, Philadelphia, Lea & Febiger, 1955, p. 601.

3. Kossman, C. E.: Personal communication to the authors.

4. Holzman, M.: Clinical Electrocardiography: A Textbook for Practitioners and Students, London, Staples Press, Ltd., 1952, p. 37.

5. Prinzmetal, M.; Goldman, A.; Massumi, R. A.; Rakita, L.; Schwartz, L.; Kennamer, R.; Kuramoto, K., and Pipberger, H.: Clinical Implications of Error in Electrocardiographic Interpre-

tation: Heart Disease of Electrocardiographic Origin, J. A. M. A. 161:138-143 (May 12) 1956.

6. Prinzmetal, M.; Shaw, C. M., Jr.; Maxwell, M. H.; Flamm, E. J.; Goldman, A.; Kimura, N.; Rakita, L.; Borduas, J-L.; Rothman, S., and Kennamer, R.: Studies on the Mechanism of Ventricular Activity: VI. The Depolarization Complex in Pure Subendocardial Infarction; Role of the Subendocardial Region in the Normal Electrocardiogram, Am. J. Med. 16:469-489 (April) 1954.

7. Kennamer, R.; Bernstein, J. L.; Maxwell, M. H.; Prinzmetal, M., and Shaw, C. M.: Studies on the Mechanism of Ventricular Activity: Intramural Depolarization Potentials in Normal Heart with Consideration of Currents of Injury in Coronary Artery Disease, Am. Heart J. 46:379-400 (Sept.) 1953.

8. Feil, H.; Cushing, E. H., and Hardesty, J. T.: Accuracy in Diagnosis and Localization of Myocardial Infarction, Am. Heart J. 15:721-738 (June) 1938.

9. Levine, H. D., and Phillips, E.: Appraisal of Newer Electrocardiography: Correlations in 150 Consecutive Autopsied Cases, New England J. Med. 245:833-842 (Nov. 29) 1951.

10. McCain, F. H.; Kline, E. M., and Gilson, J. S.: A Clinical Study of 281 Autopsy Reports on Patients with Myocardial Infarction, Am. Heart J. 39:263-272 (Feb.) 1950.

11. Myers, G. B.; Klein, H. A., and Stofer, B. E.: Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction, Am. Heart J. 36:535-575 (Oct.) 1948.

12. Rubin, H. B., and Weiss, M. J.: Diabetic Patients with Myocardial Infarction: The Diagnostic Accuracy of the Electrocardiogram, California Med. 86:254-256 (April) 1957.

13. Zinn, W. J., and Cosby, R. S.: Myocardial Infarction: II. Re-Evaluation of Diagnostic Accuracy of the Electrocardiogram, Am. J. Med. 8: 177-179 (Feb.) 1950.

14. Levy, L., II, and Hyman, A. L.: Difficulties in Electrocardiographic Diagnosis of Myocardial Infarction, Am. Heart J. 39:243-262 (Feb.) 1950.

15. Dunn, W. J.; Edwards, J. E., and Pruitt, R. D.: The Electrocardiogram in Infarction of the Lateral Wall of the Left Ventricle, Circulation 14: 549-555 (Oct.) 1956.

16. Scher, A. M.; Young, A. C.; Malmgren, A. L., and Erickson, R. V.: Activation of the Interventricular Septum, Circulation Res. 3:56-64 (Jan.) 1955.

17. Guraieb, S. R., and Rigdon, R. H.: Fibroelastosis in Adults, Am. Heart J. 52:138-148 (July) 1956.

18. Myers, G. B.; Sears, C. H., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Ring-like Subendocardial Infarction of the Left Ventricle, Am. J. M. Sc. 222:417-426 (Oct.) 1951.

19. Lepeschkin, E.: Modern Electrocardiography: Vol. I. The P-Q-R-S-T-U Complex, Baltimore, Williams & Wilkins Company, 1951, p. 440.

20. Barnes, A. R.: Electrocardiogram in Myocardial Infarction: Review of 107 Clinical Cases and 108 Cases Proved at Necropsy, Arch. Int. Med. 55:457-483 (March) 1935.

Corticotropin and Corticosteroid Therapy in Tuberculosis

ROGER M. DES PREZ, M.D., and AVRUM ORGANICK, M.D., Fort Defiance, Ariz.

Introduction

Hope of benefit from the use of corticotropin and corticosteroid in various types of bacterial infections is based on three assumptions: first, that some reactions to infections may be themselves quite harmful to the host; second, that these hormones in some poorly understood way alter or suppress host responses to infection; third, that the available antimicrobial agents are capable of controlling the infection in a host which has been so altered.

The costly aspects of some host reactions to tuberculous infection are well known. In acute wide-spread pulmonary tuberculosis the marked toxicity and at times impaired respiratory function may result in early fatality before the full effects of chemotherapy have developed. (Four cases thought to be in this category are the basis of this report.) In chronic stages replacement of parenchyma by fibrosis implies some permanent functional impairment. Caseation necrosis is locally bacteriostatic,[1] but it also may lead to subsequent bronchial dissemination. Exudative and productive defense reactions to meningeal tuberculosis may go on to subarachnoid block and hydrocephalus. The healing of infected serous membranes at times is a fibrotic and contracting process and can result in seriously compromised pulmonary or cardiac function.

Development of antimicrobial agents capable of controlling tuberculous infection made the over-all value to the host of these localizing and bacteriostatic host responses more questionable in that they may actually interfere with drug action, possibly by decreasing vascular access to infected areas but more probably by tending to change the bacterial population from the vulnerable logarithmic growth phase to the more drug-resistant stationary phase.[2]

There is fair experimental agreement that corticotropin and corticosteroids do have an anti-inflammatory, and generally deleterious, effect on animal tuberculosis.[3-6] The anti-inflammatory effect was clearly illustrated by hormone inhibition of pneumonic responses which otherwise resulted when previously sensitized animals were challenged intratracheally with solutions of tuberculin.[7] Direct visualization of tuberculous lesions in the rabbit ear indicated that the administration of corticosteroids decreased vascular damage and inhibited the exudation of cells and fluid at the infected site.[8] Some studies have not demonstrated a deleterious effect on the total course of infected animals,[9,10] and others indicated that such an effect obtained with cortisone but not with equivalent doses of corticotropin.[11-13] Studies recently completed at this institution demonstrated dissemination of infection and decreased survival time in mice treated both with cortisone and with high doses of corticotropin.[14] These observations are supported by a number of clinical instances (see below).

Several animal studies have been carried out to assay the effect of combined hormone-antibiotic therapy. Some found that concomitant administration of streptomycin only partially counteracted the detrimental

Submitted for publication Oct. 23, 1957.

From the Department of Medicine, The New York Hospital-Cornell University Medical College. Resident Fellow of the American Trudeau Society (Dr. Des Prez).

effects of corticosteroids, with an end-result that was inferior to that obtained with streptomycin treatment alone, though superior by far to results in infected animals treated with steroids alone.[15,16] Others felt that the effects of antimicrobial agents were neither potentiated nor decreased by the administration of cortisone or corticotropin [6,13,17,18] but concluded that the combination could be given safely. One very illuminating study [19] assayed the effects of cortisone and isoniazid on mouse tuberculous peritonitis with the following observations: 1. The peritoneal cavity of untreated animals contained heavily purulent material with an abundance of intracellular and extracellular bacilli. 2. Cortisone treatment produced a scanty fluid with myriads of bacilli growing in clumps and cords. 3. Isoniazid treatment was accompanied by a moderately purulent exudate, but the bacilli were almost entirely contained within phagocytic cells. 4. The combination of isoniazid and cortisone made recovery of peritoneal fluid most difficult, and the scant amount that appeared contained very little of either cells or bacilli. In combination with effective chemotherapy, which probably means a regimen containing isoniazid, the deleterious effects of steroids would seem not to obtain.

The dramatic symptomatic improvement effected by corticotropin in other infectious diseases led to its early trial in human tuberculosis.[20,21] Abrupt decrease in fever and toxicity, increase in appetite and sense of well-being, and in some cases improvement in roentgenographic findings and the extent of laryngeal involvement were noted. With withdrawal of the hormone the clinical state returned to pretreatment levels after a sometimes marked "rebound" elevation of temperature. The periods of treatment were brief, and it was not clear whether or not the hormone administration had had an untoward effect on the clinical courses as a whole. However, there soon began to appear case reports of rapid exacerbation of latent tuberculosis during hormone treatment for other disorders.[4,22-26] This still-growing group is strong evidence for the untoward effect of corticotropin and corticosteroids on human tuberculosis in the absence of concomitant effective chemotherapy.

Because of the early experimental and clinical evidence described above, there has been great caution exercised in attempting to exploit the possible benefits of steroid therapy, even though it was appreciated that the hormones probably did not interfere with the action of the antimicrobial agents. Nevertheless, there is presently recorded in the literature a surprisingly large number of cases of various types of human tuberculosis treated with combination hormone-antimicrobial therapy. Because of the possibility of avoiding subarachnoid block and diminishing endarteritis, corticotropin was early suggested for use in the treatment of tuberculous meningitis,[27] and this use seems now to be fairly well established.[28-32] Hypersensitivity reactions to antituberculous agents were treated with corticotropin in 21 cases of pulmonary tuberculosis in England,[33] with the dual result of successful reversal of the drug sensitivity and in most cases remarkably rapid improvement in the status of the tuberculosis. Early French and Italian interest and success in corticotropin and corticosteroid treatment of serous membrane tuberculosis led to extensive trials in a wide variety of types of infection, including meningeal, endobronchial, cutaneous, pleural, and pericardial tuberculosis; extremely toxic states; pulmonary tuberculosis, and even pleural effusions complicating therapeutic pneumothorax. In one issue of the *Revue de la Tuberculose* a total of almost 500 cases of various types of tuberculosis treated with hormones and antimicrobial agents was reported, with follow-up extending to three years in some series.[31,32,34-41] In general the results were excellent. The most cogent point to be learned from this large clinical experience is that there were no manifest deteriorations (appearance of miliary or meningeal spread, or reversion

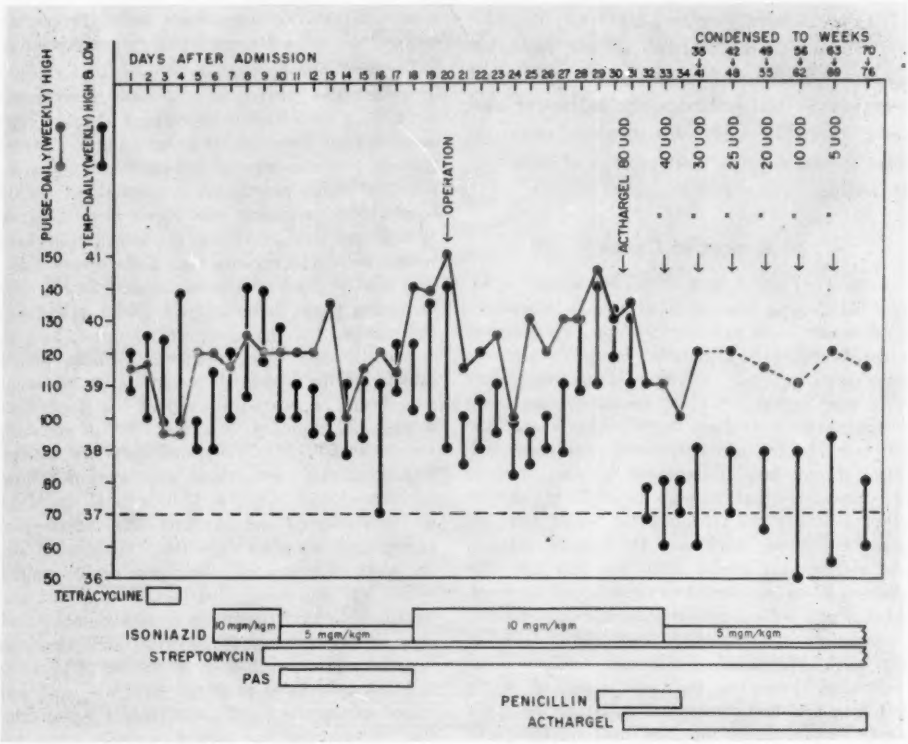
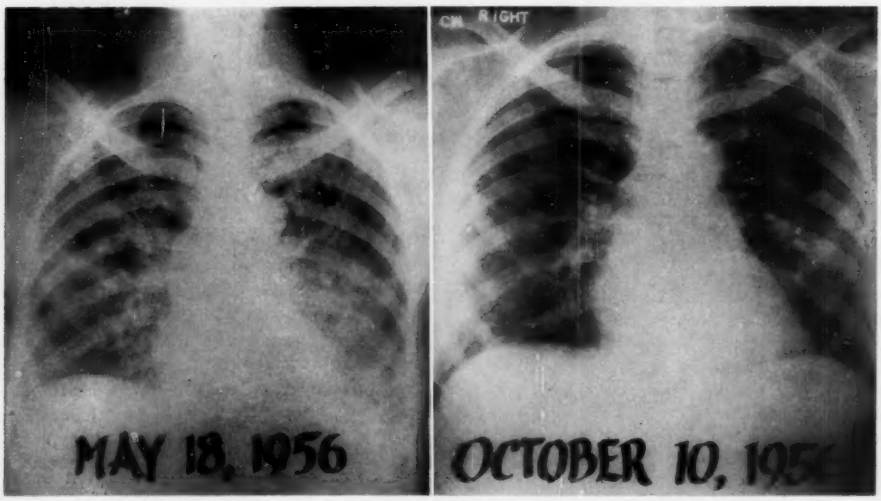


Fig. 1 (Case 1).—Daily temperatures, pulse rates, and medications received.

Fig. 2 (Case 1).—Marked roentgenographic improvement of extensive infiltrates over a five-month interval.



of a previously negative sputum to positive) in clear relationship to the hormone therapy. Corticotropin and cortisone would seem to be safe therapeutic adjuncts and most probably very worth-while ones, at least in some types and phases of tuberculous disease.

Report of Cases

CASE 1 (Figs. 1 and 2).—The patient, a 44-year-old Negro woman, had been in essentially good health until two weeks prior to admission, when she noted mild headache, feverish sensations, generalized myalgias, and malaise appearing over a 12-hour period. A chest roentgenogram taken elsewhere showed slight hazy infiltration at the left heart border, and tetracycline was prescribed. After several days of treatment with no relief of symptoms the patient was admitted to another hospital, where she remained one week, noted no improvement on continuing tetracycline therapy, and left against advice when she was told that she was to be transferred to the tuberculosis ward. At that time a chest roentgenogram showed marked progression in comparison with the film taken two weeks previously. There was confluent dense infiltration throughout the lower one-third of the left lung field and patchy infiltration involving the lower two-thirds of the lung field on the right. She was accordingly referred to The New York Hospital for admission.

The past history was negative, save for an attack of malaria at age 10 and two episodes of unexplained epigastric pain several years previously which had necessitated hospitalization.

Admission physical examination described a well-developed and nourished mildly ill Negro woman in no distress. The temperature was 39 C (102.2 F); pulse, 100; respirations, 17, and blood pressure, 118/78. The positive physical findings were confined to the lower one-half of the left lung field posteriorly, where dullness to percussion, moist inspiratory rales, bronchial breath sounds, and slightly decreased tactile fremitus were noted.

Admission laboratory data included the following: urinalysis, specific gravity 1.020; Benedict's test, 4+ positive for reducing substances; albumin, 0; red blood cells and white blood cells, 2 to 4 each per high-power field; white blood cell count, 5100; differential, 24% lymphocytes, 3% monocytes, 70% mature polymorphonuclear leukocytes, 3% band forms, and 2% metamyelocytes; fasting blood sugar, 154 mg. per 100 cc.; blood urea nitrogen, serum calcium, alkaline phosphatase, phorphorus, bilirubin, cephalin-cholesterol flocculation, and total protein with albumin-globulin ratio, all within normal limits. On the day after admission acid-fast organisms were found in sputum concentrate, and culture was subsequently positive.

The first five hospital days were characterized by progressive symptoms, with daily fever peaks to 39.5 C (103.1 F), the appearance of moist rales over the right base quickly progressing to signs of consolidation, the onset of left-lower-chest pleuritic pain, and mildly progressive dyspnea. On the sixth hospital day treatment was begun, with isoniazid at a dosage level of 10 mg. per kilogram of body weight per day, a regimen then under investigation. The clinical state continued to deteriorate, with increasing fevers (temperature to 40.5 C [104.9 F]), tachycardia, tachypnea, severer dyspnea, and increasingly severe pleuritic pain. Because of the gravity of the illness, three days after treatment was begun a standard regimen of triple-drug therapy at standard dosage levels of isoniazid, aminosalicylic acid (PAS), and daily streptomycin was substituted, with slight improvement following this change. On the 18th hospital day PAS was discontinued and isoniazid was increased to 10 mg. per kilogram. On the 20th hospital day the onset of severe epigastric pain similar to that which had occasioned hospitalizations in the past led to exploratory laparotomy, with negative findings. Postoperatively the systemic and pulmonary symptoms progressed, with increasing tachycardia, tachypnea, dyspnea, profound weakness, and continued spiking fevers. Efforts to find causes other than tuberculosis for this profoundly toxic and progressive illness were unsuccessful. On the 32d hospital day treatment was begun with repository corticotropin injection (ACTH Gel), 40 units twice daily. Within eight hours of the initial injection of corticotropin the fever, weakness, dyspnea, and tachypnea dramatically disappeared. Chest roentgenogram at this time showed further progression, with infiltrations scattered throughout both lung fields.

The subsequent course has been one of progressive radiologic and clinical improvement. Repository corticotropin injection was tapered and finally discontinued on the 69th hospital day, with transient temperature elevation to 38 C (100.4 F) but no serious rebound phenomena. An incidental episode was a second attack of epigastric pain, during which a rise in serum amylase to 150 units and the finding of pancreatic calcification on abdominal roentgenogram confirmed the previous impression of chronic relapsing pancreatitis. Cultures of gastric aspirates have been negative for tubercle bacilli since the third month of treatment. The patient was discharged after eight months of therapy, at which time there were no symptoms and the chest roentgenogram was virtually normal. She is still taking combined isoniazid-streptomycin.

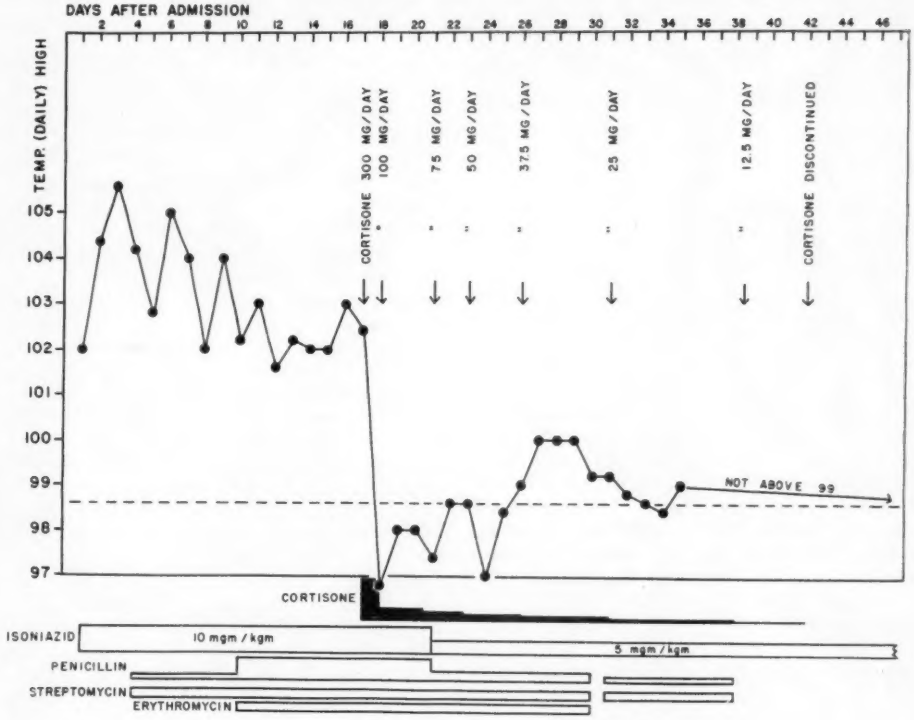
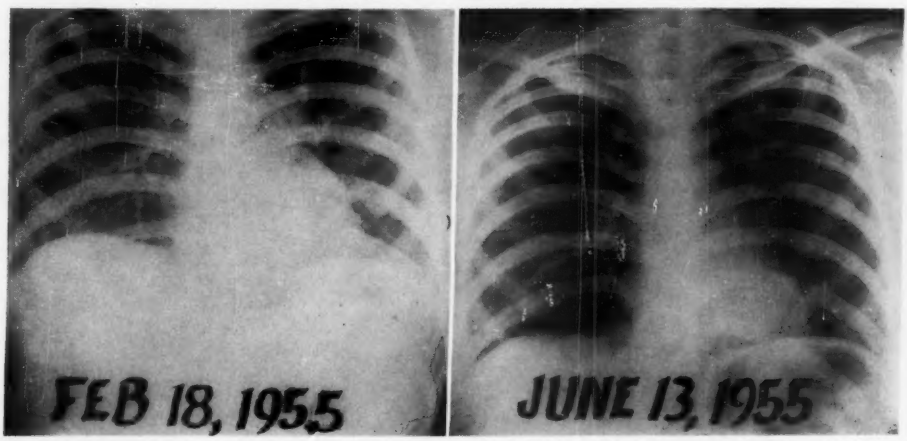


Fig. 3 (Case 2).—Daily temperatures and medications received.

Comment.—In this case an optimal chemotherapeutic regimen was instituted within three weeks of the initial symptoms of tuberculosis. In spite of this, the patient's course continued increasingly toxic to the point that six weeks after the onset of symptoms and four weeks after the initiation of treatment the fever, tachypnea, dyspnea, and tachycardia seemed a threat to life. The immediate symptomatic remis-

Fig. 4 (Case 2).—Roentgenographic clearing of miliary infiltrates in four months.



sion with the institution of corticotropin was most dramatic. The fact that this response was produced by corticotropin makes it unlikely that adrenal exhaustion or insufficiency was responsible for the grave clinical state. No less gratifying than the immediate improvement is the long-term excellent result.

CASE 2 (Figs. 3 and 4).—The patient, a 19-year-old Navajo woman, was transferred to the Navajo Medical Center Tuberculosis Sanatorium from another hospital because of fever and a chest roentgenogram suggestive of miliary tuberculosis. The illness dated to two months previously, when, during the eighth month of pregnancy, she noted cough and malaise and had one episode of hemoptysis. After delivery, four weeks later, she became febrile. The chest roentgenogram did not become abnormal until three weeks after the development of fever, when it revealed finely nodular disseminated infiltrations suggesting miliary tuberculosis, and accordingly the patient was transferred to the sanatorium.

Admission physical examination revealed a well-nourished and well-developed young woman looking moderately ill, with rapid respirations and a temperature of 102 F. A few moist rales were heard over the right lung base posteriorly. There were no organs palpable in the abdomen, and no tenderness was present. There was a slightly foul-smelling bloody lochia.

Admission laboratory data included the following: urinalysis, specific gravity 1.001; albumin, 0; Benedict's test for reducing substances, 0; microscopic examination, 8 to 12 white blood cells and occasional bacteria; repeat urinalysis of a catheterized specimen, negative on microscopic examination and on culture; hemoglobin, 8.5 gm. per 100 cc.; hematocrit, 29%; white blood cell count, 4000; differential count, 16% lymphocytes, 3% monocytes, and 81% polymorphonuclear leukocytes; lumbar puncture, fluid clear and colorless, no cells; sugar, protein, and chlorides, all within normal limits; sputum, positive on smear for tubercle bacilli.

A diagnosis of miliary tuberculosis was made, and on the day of admission treatment was started with isoniazid at a dosage level of 10 mg. per kilogram per day. The first hospital days were marked by fever peaks to over 105 F and the appearance of rales at both lung bases and over the front of the chest. The uterine lochia continued blood-tinged and slightly purulent, and on the fourth hospital day procaine penicillin, 300,000 units, and streptomycin, 0.5 gm., given intramuscularly twice daily, were added to the treatment to cover the possibility of a concomitant puerperal endometritis. Culture of the lochia subsequently was reported as showing Staphylococcus pyogenes var. aureus, and because of this on the 10th hospital day penicillin was increased to 1,000,000 units (aqueous) every two hours and erythromycin was added in doses of 200 mg. every six hours. On the 11th hospital day a gynecological consultant found the uterus to be normally involuting and only slightly tender and felt that the findings were those only of a low-grade infection. The course continued to be one of persisting high temperatures, increasing rales, and increasing weakness. Supportive blood transfusions were given on the 2d, 8th, and 17th hospital days without appreciable effect. On the 17th hospital day treatment was begun with cortisone, 300 mg. over a 24-hour period and then 100 mg. daily. Defervescence was abrupt, and there was prompt subjective improvement. The subsequent course was benign, save for slight temperature elevations associated with decreases in doses of cortisone and also of isoniazid. The cortisone dosage of 100 mg. daily was maintained for one week and then gradually reduced and was discontinued after 26 days. Uterine lochia ceased completely by the 34th hospital day, and staphylococci were no longer culturable from the vagina. Penicillin, streptomycin, and erythromycin were discontinued on the 41st hospital day. Chest roentgenograms six months after the initiation of therapy showed complete clearing. Cultures for tubercle bacilli were positive through four months of treatment but have been negative subsequently. The patient was discharged 16 months after admission and is still taking isoniazid.

Comment.—In this case of miliary tuberculosis corticosteroids were used because in spite of three weeks of adequate chemotherapy the clinical condition seemed to be deteriorating dangerously. Relief of symptoms and defervescence were immediate, and the total course has been excellent, with sputum conversion after five months of treatment and complete roentgenographic clearing in six months. The complicating endometritis does not appear to have been a major factor in her course, since at no time could significant uterine enlargement or tenderness be demonstrated.

CASE 3 (Figs. 5 and 6).—The patient, a 13-year-old Navajo girl, was admitted to the Navajo Medical Center with a history of sore throat, cough, and weakness of one month's duration.

Admission physical examination revealed a wasted and acutely ill adolescent girl, coughing frequently and complaining of sore throat. The pulse was 120; blood pressure, 80/60; temperature,

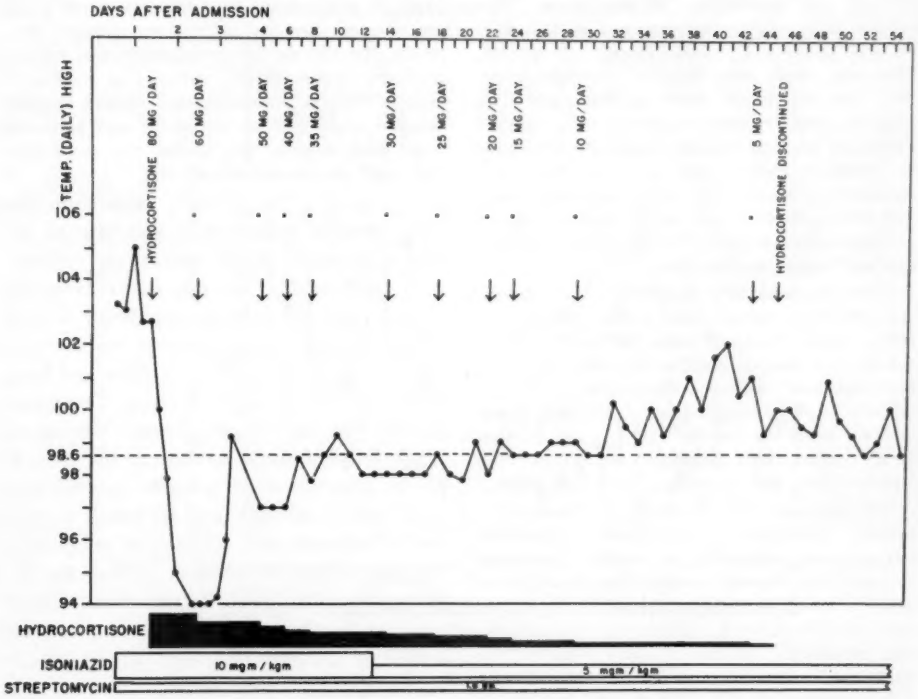
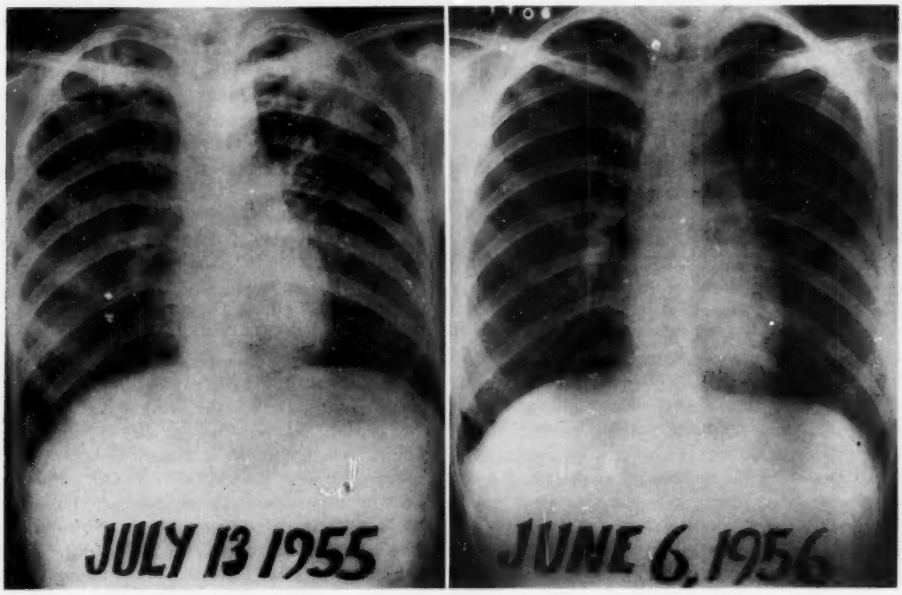


Fig. 5 (Case 3).—Daily temperatures and medications received.

Fig. 6 (Case 3).—Marked roentgenographic improvement of disseminated infiltrates in 12 months.



103.2 F, and respirations, 68 per minute. This extreme tachypnea was accompanied by flaring of the alae nasae, and central cyanosis was present. The optic fundi were free of choroidal tubercles. The soft palate, posterior pharyngeal wall, epiglottis, and arytenoid eminences were involved with small areas of grayish ulcerations surrounded by reddened swollen mucosa. The chest was resonant, but course rales and rhonchi were heard over all lung fields. There was no lymphadenopathy or hepatosplenomegaly. The neurologic examination was within normal limits.

Admission laboratory data included the following: urinalysis, normal; hemoglobin, 11.0 gm. per 100 cc.; white blood cell count, 7600, with a normal differential; sputum, positive on smear for acid-fast organisms; culture, subsequently positive for tubercle bacilli; roentgenogram of the chest showed multiple small cavities up to 1 cm. in diameter in both apices, with a superimposed diffuse finely nodular infiltration throughout both lung fields.

The impression on admission was far-advanced chronic pulmonary tuberculosis, tuberculous laryngitis and pharyngitis, and widely disseminated laryngeal-bronchogenic spread. The possibility of a superimposed hematogenous miliary tuberculosis could not be excluded. Oxygen by nasal catheter was immediately administered, and treatment was begun with isoniazid at dosage levels of 10 mg. per kilogram per day and streptomycin, 1.0 gm. intramuscularly daily. The following day increasing cyanosis and more labored respiratory movements (use of the neck muscles and retraction of the jaw with inspiration) gave evidence of increasing respiratory insufficiency, and the temperature reached a peak of 105 F. Treatment was then begun with hydrocortisone, 80 mg. daily. Defervescence was immediate, and over the following week there was marked easing of respirations, improvement in color, and some clearing of the rales. During the succeeding four weeks the course was afebrile; the chest became completely clear to auscultation, and marked decrease in the swelling and erythema of the laryngeal and pharyngeal lesions was noted. Over this period hydrocortisone was being steadily reduced by small decrements. In the sixth hospital week temperature elevations were again noted (to a high of 101.4 F); the patient complained of some aching and headache, and increased redness of the previously almost healed palatal lesions was noted. A chest roentgenogram at this time revealed that previously scattered nodular infiltrations had become confluent in the left apex and to less extent in the right. Because of the question of symptomatic and roentgenographic deterioration, the then small dose (5 mg.) of hydrocortisone was discontinued entirely on the 49th hospital day. The temperature subsided gradually over the following two weeks. Isoniazid was reduced to a dosage level of 5 mg. per kilogram per day on the 16th hospital day; on the 71st hospital day streptomycin was reduced to 1 gm. thrice weekly. After nine months of therapy the chest roentgenogram showed virtually complete clearing on the left and a small persisting right apical density. The sputum was never positive after the admission specimen.

Comment.—The primary indication for corticosteroid treatment in this case of extensive recently spread pulmonary tuberculosis presumably secondary to laryngeal disease was the critical respiratory insufficiency, a situation aggravated by the very high temperatures. The immediate and long-term results have been excellent. The roentgenographic and clinical changes during the sixth hospital week seemed at the time to be an expression of possible deterioration with use of steroids, and the small dose of hydrocortisone was withdrawn completely. An alternative explanation is that the hydrocortisone had been decreased too rapidly and the result was an escape from steroid effect of an infection not yet completely under antimicrobial control.

CASE 4 (Fig. 7).—A 45-year-old white doorman was admitted to The New York Hospital on March 11, 1957, because of shortness of breath and fever. In a setting of excellent health, six weeks prior to admission the patient noted easy fatigability and mild breathlessness on exertion, which were progressive. Three weeks later these symptoms were sufficiently severe to confine him to bed, and he noted onset of cough, production of yellow sputum in small amounts, and night sweats. For several days prior to admission mild pain on swallowing was present. Over the six-week period there was a 35 lb. weight loss.

Admission physical examination revealed a somewhat wasted severely ill white man. Temperature was 39.4 C (102.9 F); pulse, 140; respirations, 36, and blood pressure, 110/70. There was mild cyanosis of the lips and nail beds. No choroidal tubercles were seen on fundoscopic examination. Over the right posterior buccal mucosa there was a 2 cm. patch of flat, dull, grayish exudate. Indirect laryngoscopy revealed a somewhat reddened protuberance between the arytenoid cartilages. Thoracic configuration was normal. Tachypnea and dyspnea were present at rest, and there was vigorous inspiratory contraction of the neck muscles and inspiratory retraction of the supraclavicular and intercostal spaces. Moist course inspiratory rales were heard over all lung fields.

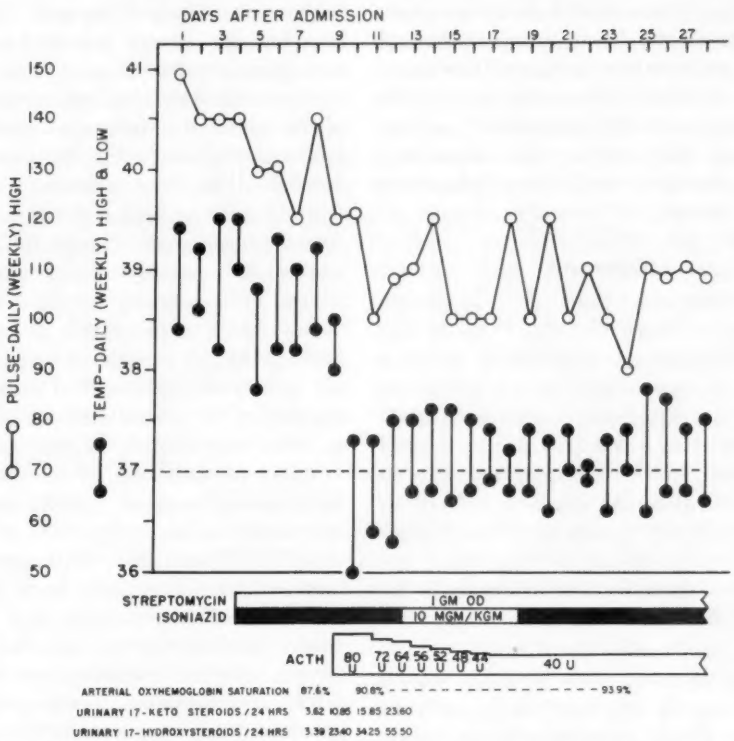

DAYS AFTER ADMISSION
1 3 5 7 9 11 13 15 17 19 21 23 25 27
PULSE-DAILY (WEEKLY) HIGH
TEMP-DAILY (WEEKLY) HIGH & LOW
150 140 130 120 110 100 90 80 70 60 50
41 40 39 38 37 36
STREPTOMYCIN
ISONIAZID
1 GM OD
10 MGM/KGM
ACTH
80 72 64 56 52 48 44
U U U U U U U
40 U
ARTERIAL OXYHEMOGLOBIN SATURATION 87.6% 90.8% 93.9%
URINARY 17-KETO STEROIDS/24 HRS. 3.62 10.85 15.85 23.60
URINARY 17-HYDROXYSTEROIDS/24 HRS. 3.39 23.40 34.25 55.50

Fig. 7 (Case 4).—Daily temperatures and medications received. At the bottom of the graph appear the changes in blood oxyhemoglobin saturation and in urinary 17-keto- and 17-hydroxysteroids which occurred coincident with corticotropin therapy.

The heart was not enlarged; the rate was rapid and regular, and sounds were of good quality. No murmurs were heard. A firm, sharp, smooth, nontender liver edge was palpated 4 fingerbreadths below the right costal margin. The spleen was not palpable; pedal edema was not present, and neurologic examination was unremarkable.

Admission laboratory data included the following: urinalysis, specific gravity 1.020; reaction, 5.0; albumin, 2+; Benedict's test for reducing substances, negative; red blood cells, 5 to 7, and white blood cells, 10 to 20 per high-power field; hematocrit, 48%; red blood cell count, 6,000,000; white blood cell count, 13,400, with 14% lymphocytes, 6% monocytes, 1% eosinophils, 1% basophils, 38% polymorphonuclear leukocytes, mature forms, and 40% band forms; red blood cells and platelets normal on smear; BUN, fasting blood serum, CO_2, chloride, sodium, potassium, calcium, alkaline phosphatase, bilirubin, and total protein with albumin-globulin ratio all within normal limits. Sputum was positive for tubercle bacilli on smear and subsequently on culture. Chest roentgenogram revealed nodular infiltrations throughout both lung fields, tending to confluence at the bases.

The diagnostic impression was far-advanced pulmonary tuberculosis, pharyngeal and laryngeal tuberculosis, and extensive recent laryngeal bronchogenic spread. On the third hospital day treatment was begun with isoniazid (10 mg. per kilogram per day) and daily streptomycin. The continuing marked toxicity and signs of respiratory insufficiency were felt to indicate the addition of corticotropin to the regimen on the eighth hospital day. Arterial oxyhemoglobin saturation and urinary corticosteroid excretion products were determined immediately prior to beginning this therapy and at intervals thereafter (Fig. 7*). The response to corticotropin was immediate, and the patient's clinical condition remains very satisfactory.

Comment.—Reference to Figure 7 will demonstrate the measured reversal of hypoxia with corticotropin therapy observed in this patient.

*Dr. Daniel Lukas did the determination of blood oxyhemoglobin saturation.

Urinary 24-hour steroid excretion products were at the lower limits of normal prior to corticotropin therapy. After corticotropin stimulation these rose in a fashion typical of normally responsive adrenal glands. In this case at least laboratory evidence indicates that adrenal exhaustion was not present.

Comment

Use of Hormone Therapy (Corticotropin and Corticosteroids) in Toxic States.—In the above cases the addition of hormone therapy appears to have been a life-saving measure, an experience similar to those recorded by others in a considerable number of patients.[32,34,35,40] Special attention is again directed to the dramatic reversal of acute respiratory insufficiency which characterized the responses of Cases 1, 3, and 4 and the laboratory demonstration of reversal of hypoxia in the last of these.

Hormone Therapy in Meningitis.—It is this form of tuberculosis in which the use of corticotropin was first suggested.[27] An abundant clinical experience has confirmed that corticotropin therapy effects prompt clinical improvement, seems to prevent the development of subarachnoid block, at times is effective in reversing a previously established block, and is associated with early reversal of cerebrospinal fluid abnormalities.[28-32,42] It is likely that the vasculitis which at times results in irreversible nerve tissue damage is also ameliorated. On the basis of his results one observer feels that the early institution of hormone therapy may well obviate the necessity of intrathecal therapy.[29]

Hormone Treatment of Hypersensitivity to Antituberculous Chemotherapeutic Agents.—Loss of one or another of the major antituberculous drugs for reasons of drug reactions may well be critical in individual cases. In one series of 21 carefully studied patients[33] various untoward drug reactions were successfully reversed by concomitant corticotropin therapy, and in many cases the reactions did not recur when the hormone was discontinued. Indications in a few cases were extended to include mere gastric intolerance of PAS. There were no deteriorations, and in the opinion of the author the courses of many of the patients were benefited aside from the suppression of the drug reaction.

Hormone Treatment of Tuberculosis of Serous Membranes.—Though the course of tuberculous pleurisy with effusion is thought to be generally favorable with drug therapy alone, a proportion of cases have fairly prolonged periods of sizable effusion and pulmonary collapse.[43] Thickening and scarring of the pleural surfaces may result, at times necessitating surgical procedures to effect reexpansion. French and Italian investigators have had considerable experience in the use of corticotropin in this situation[36,38-40,45] and feel that the results have been uniformly good, with quick disappearance of the effusion and excellent long-term results. Several cases are recorded in which pleural effusions occurring during therapeutic pneumothorax and complicating pneumonolysis have resorbed with corticosteroid and corticotropin therapy, making maintenance of the pneumothorax possible.[39,46] Even chronic cases with contracted lungs and pleural effusions of long standing have also in some instances responded excellently.

In tuberculous pericarditis the question of hormone therapy is even more important. Prior to effective chemotherapy the mortality from proven tuberculous pericarditis was variously quoted as between 50% and 80%.[47-51] In roughly one-half of the cases death was due to disseminated infection, and in the other half, to cardiovascular effects of an acute or chronic nature. With the presently available drugs it is probably justifiable to hope that overwhelming infection following pericarditis is no longer a problem. However, it is not possible to assume that the chronic cardiovascular complications will be similarly obviated by effective chemotherapy, and, indeed, there is some recent evidence to indicate the con-

trary.[52-56] The poor prognosis of constrictive pericarditis from a cardiovascular point of view has led some leading surgeons to advocate early pericardiectomy in the stage of effusion if signs of heart failure persist under treatment.[57,58] If a small percentage of cases of tuberculous pericarditis should go on to constriction with use of early and optimum chemotherapy and if the concomitant institution of hormone therapy would prevent this chronic scarring, then a case could be made for the routine administration of combined hormone-antimicrobial therapy as a conservative alternative to possible future pericardiectomy. Both of the premises on which this conclusion is based remain to be tested.

Hormone Therapy in Endobronchial Tuberculosis.—There is general agreement that hormone therapy has little or no effect on tuberculous mediastinal adenitis. However, the obstruction in endobronchial tuberculosis which results in atelectasis and subsequent pneumonitis is in part due to mucosal turgescence and hyperemia. This portion at least seems to be reversible by hormone therapy, and dramatic results have been recorded both in adults[41] and in children.[35,59]

Hormone Therapy in Uncomplicated Pulmonary Tuberculosis.—Experience with hormone therapy is most extensive in pulmonary tuberculosis.[32,33,36,44] There is not general agreement as to whether or not the results obtained are superior to the results of chemotherapy alone, contrary to the situation in the extrapulmonary forms. In no series, however, were the results thought to be worse. Recent lesions of predominantly exudative character showed the most marked response, but in several cases of chronic caseocavitary disease long-term courses which had remained static for protracted periods showed considerable roentgenographic improvement.

Choice of Agent and Duration of Therapy.—Various observers have been unable to determine any clear-cut difference between the clinical results obtained with corticotropin and with cortisone. That adrenal insufficiency or "exhaustion" contributes to the toxicity of a given case of tuberculosis is certainly possible, but in view of the similarity of the responses to corticotropin and corticosteroid this would seem to be an infrequent occurrence. There are some experimental data which indicate that corticotropin (ACTH) has a less deleterious effect on untreated experimental tuberculosis.[11-13] Studies are under way[5] to define more precisely the differing effects of different adrenal and pituitary products on tuberculous infection. Until this more definitive information is available, however, it seems probably advisable to choose corticotropin. Doses successfully used have varied from 20 to 80 units daily, and treatment has generally been continued for from one to three months. The advantages of discontinuing hormone therapy as soon as the treatment objectives have been secured are well known, and the advisability of doing so gradually and, in the case of corticosteroid, of stimulating the adrenal with corticotropin at the end of the course applies here as in all cases of chronic hormone administration.

Effect of Hormone Therapy on Development of Immunity.—Steroid therapy causes diminution or disappearance of the reaction to cutaneous tuberculin in over one-half of the cases so treated. It is doubtful that this alteration of the tuberculin reaction implies either a concomitant antibody decrease or an inhibition of the immunologic response to infection.[5,60] One very interesting animal study[61] reported the unexpected result that a group of mice which received BCG while being given steroid treatment subsequently (after discontinuation of steroids) demonstrated resistance to challenge with virulent tubercle bacilli superior to that of a group immunized in the same manner but receiving no steroids. The inference is that the development of resistance was at least not hampered by steroid treatment during the period of the immunizing infection.

Chemotherapeutic Status at Time of Steroid Treatment.—Only one study[40] noted that the less favorable results of hormone therapy occurred in cases infected with organisms demonstrating drug resistance. However, it seems likely that in drug-resistant infections hormone therapy could be as dangerous as it has proved in cases of untreated infection. Since a small number of primarily drug-resistant infections do occur, the assumption that absence of prior antimicrobial therapy indicates a drug-sensitive infection carries a certain risk, but at the present time it is probably slight.[62]

Summary and Conclusions

Disadvantages of certain host reactions to tuberculous infection have led to the attempt to suppress these reactions by corticotropin and corticosteroid therapy when given with effective antimicrobial treatment. A portion of the experimental and clinical evidence supporting this position is reviewed. Four cases of widespread pulmonary tuberculosis with severe toxicity, two of which were complicated by marked respiratory insufficiency, are reported in which use of steroids appears to have been a crucially successful measure, and other situations are cited in which it was described as having advantage. It is concluded that in combination with effective antimicrobial therapy use of corticotropin and cortisone in tuberculosis is safe; that in cases with marked toxicity, in complicated tuberculous meningitis, and in severe reactions to antituberculous chemotherapeutic agents there are definite and sometimes urgent indications for their administration, and that their use in serous membrane tuberculosis, endobronchial tuberculosis, and uncomplicated pulmonary tuberculosis seems promising and deserves further trial.

Dr. Carl Muschenheim suggested this report and gave encouragement and advice during its completion.

Fort Defiance Indian Sanatorium.

REFERENCES

1. Hirsch, J. G.: Biochemical Factors Which May Influence the Fate of Tubercle Bacilli in Tissues, in Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and Host, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little, Brown & Company, 1955, p. 115.

2. Mitchison, D. A., and Selkon, J. B.: The Bactericidal Activities of Antituberculous Drugs, Am. Rev. Tuberc. 74:109 (Pt. 2), 1956.

3. Hart, P. D'A., and Rees, R. J. W.: Enhancing Effect of Cortisone on Tuberculosis in the Mouse, Lancet 2:391, 1950.

4. Johnson, J. R., and Davy, W. N.: Cortisone, Corticotropin, and Antimicrobial Therapy in Tuberculosis in Animals and Man: Review, Am. Rev. Tuberc. 70:623, 1954.

5. Lurie, M. B., and Zappasodi, P.: On the Mode of Action of Cortisone on the Pathogenesis of Tuberculosis and Its Implications for the Nature of Genetic Resistance to the Disease, in Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and Host, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little, Brown & Company, 1955, p. 246.

6. Morgan, T. E.; Wanzer, S. H., and Smith, D. T.: The Effect of Cortisone and Streptomycin on Experimentally Induced Pulmonary Tuberculosis in Rabbits, J. Bact. 67:257, 1954.

7. Reinmuth, O. M., and Smith, D. T.: The Effect of Adrenocorticotropic Hormone (ACTH) on Pneumonia Induced with Tuberculin in the Lungs of Sensitized Rabbits, Am. Rev. Tuberc. 64:508, 1951.

8. Ebert, R. H.: In Vivo Observations on the Effect of Cortisone on Experimental Tuberculosis, Using the Rabbit Ear Chamber Technique, Am. Rev. Tuberc. 65:64, 1952.

9. Karlson, A. G., and Gainer, J. H.: Influence of Cortisone on Experimental Tuberculosis of Guinea Pigs, Dis. Chest 20:469, 1951.

10. Weimer, H. E.; Boak, R. A.; Bogan, E.; Drusch, H. E.; Miller, J. N.; Moshin, J. R., and Carpenter, C. M.: Comparative Effects of Corticotropin and Cortisone on Experimental Tuberculosis, Am. Rev. Tuberc. 68:31, 1953.

11. LeMaistre, C., and Tompsett, R.: The Evolution of Tuberculous Lesions in the Guinea Pig During Administration of Adrenocorticotropic Hormone (ACTH) or Cortisone, Am. Rev. Tuberc. 64:295, 1951.

12. Youmans, G. P., and Youmans, A. S.: The Effect of Hormonal Preparations on the Survival of Mice Injected Intravenously with Virulent, Attenuated, and Avirulent Mycobacteria, Am. Rev. Tuberc. 69:790, 1954.

13. Wanzer, S. H.; Morgan, T. E., and Smith, D. T.: The Effect of Corticotropin (ACTH) and

Streptomycin on Experimentally Induced Pulmonary Tuberculosis in Rabbits, J. Bact. 67:264, 1954.

14. Batten, J. C., and McCune, R. M.: The Influence of Corticotropin and Certain Corticosteroids on Microbial Populations (M. Tuberculosis) in Tissues of Mice, to be published.

15. Molomut, N., and Spain, D. M.: Effect of a Minimal Dose of Cortisone Combined with a Subeffective Dose of Dihydrostreptomycin on Experimental Guinea Pig Tuberculosis, Am. Rev. Tuberc. 67:101, 1953.

16. Cummings, M. M.; Hudgins, P. C.; Whorton, M. C., and Sheldon, W. H.: The Influence of Cortisone and Streptomycin on Experimental Tuberculosis in the Albino Rat, Am. Rev. Tuberc. 65:596, 1952.

17. Bunn, P. A., and Robinson, F. O.: Effects of Decreasing Dosages of Corticotropin upon the Course of Ocular Tuberculosis in the Rabbit, Am. Rev. Tuberc. 69:1051, 1954.

18. Batten, J. C., and McCune, R. M.: The Influence of Corticotropin and Cortisone with Antituberculous Drugs on Microbial Populations (M. Tuberculosis) in Tissues of Mice, to be published.

19. Ilavsky, J., and Foley, E. J.: Studies on the Effect of Cortisone with Chemotherapeutic Agents on Tuberculous Peritonitis in Mice, Antibiotics & Chemother. 4:1068, 1954.

20. Freeman, S.; Fershing, J.; Wang, C., and Smith, L.: The Effect of ACTH on Patients with Pulmonary Tuberculosis, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1950, p. 509.

21. LeMaistre, C.; Tompsett, R.; Muschenheim, C.; Moore, J., and McDermott, W.: Effects of Adrenocorticotropic Hormone and Cortisone in Patients with Tuberculosis, J. Clin. Invest. 30:445, 1951.

22. Walker, B.: Miliary Tuberculosis in a Case of Acute Disseminated Lupus Erythematosus Treated with A. C. T. H., Brit. M. J. 2:1076, 1952.

23. Traut, E. F., and Ellman, J.: Exacerbation of Tuberculosis During Treatment with Cortisone, J. A. M. A. 149:1214, 1952.

24. Harris-Jones, J. N., and Pein, N. K.: Disseminated Lupus Erythematosus Complicated by Miliary Tuberculosis During Cortisone Therapy, Lancet 2:115, 1952.

25. Davidson, A. G.; Fox, L., and Gold, J. J.: Appearance of Miliary Tuberculosis Following Therapy with ACTH and Cortisone in a Case of Acute Disseminated Lupus Erythematosus, Ann. Int. Med. 38:852, 1953.

26. Hill, H. M., and Kirshbaum, J. D.: Miliary Tuberculosis Developing During Prolonged Cortisone Therapy of Systemic Lupus Erythematosus, Ann. Int. Med. 44:781, 1956.

27. Kinsell, L. W.: The Clinical Application of Pituitary Adrenocorticotropic and Adrenal Steroid Hormones, Ann. Int. Med. 35:615, 1951.

28. Bulkeley, W. C. M.: Tuberculous Meningitis Treated with A. C. T. H. and Isoniazid: Comparison with Intrathecal Streptomycin, Brit. M. J. 2:1127, 1953.

29. Ashby, M., and Grant, H.: Tuberculous Meningitis Treated with Cortisone, Lancet 1:65, 1955.

30. Johnson, J. R.: Tuberculous Meningitis: Use of Corticotropin as an Adjunct to Chemotherapy, Am. Rev. Tuberc. 72:825, 1955.

31. Fouquet, J.; Teyssier, L.; Heimann, V.; Leonardon, V., and Cazès, M.: Les Thérapeutiques anti-inflammatoires dans la méningite tuberculeuse: Étude de 15 cas, Rev. tuberc., Paris 19:1303, 1955.

32. Mattéi, C.; Laval, P.; Vincent, P.; Balozet, P.; Choux, J.; Saby, and Ruf, G.: Hormones corticotropes dans la tuberculose pulmonaire et la tuberculose méningée, Rev. tuberc., Paris 19:1315, 1955.

33. Houghton, L. E.: Combined Corticotrophin Therapy and Chemotherapy in Pulmonary Tuberculosis, with Special Reference to Hypersensitive Reactions, Lancet 1:595, 1954.

34. Barré, E., and Lucas, J. C.: Bilan de 2 années d'hormonothérapie dans la tuberculose pulmonaire, Rev. tuberc., Paris 19:1368, 1955.

35. Breton, A.; Gaudier, B., and Walbaum, R.: Essais de corticothérapie général associée aux antibiotiques antibacillaires dans le traitement de la tuberculose de l'enfant, Rev. tuberc., Paris 19:1373, 1955.

36. Even, R.; Sors, C.; Delaude, A.; Roujeau, J.; Trocmé, Y., and Commare, G.: La Place des hormones hypophyso-surrénales dans le traitement de la tuberculose: Étude clinique, anatomo-pathologique et expérimentale, Rev. tuberc., Paris 19: 1249, 1955.

37. Mannes, P.; Lederer, J.; Derriks, R., and Nicaise, R.: Le Traitement de certaines formes de tuberculose pulmonaire par l'association hormones hypophyso-surrénaliennes et antibiotiques, Rev. tuberc., Paris 19:1323, 1955.

38. Bruel, R.; Duval, C.; Amouroux, P.; Lestage, J.; Guin, J., and Tafani, A.: La Liberté pleurale après traitement des pleurésies séro-fibreneuses par L'A. C. T. H., Rev. tuberc., Paris 19:1332, 1955.

39. Catta, J.; Mercier, A., and Herve du Penhoat, A.: L'A. C. T. H. associé aux antibiotiques chez les tuberculeux pulmonaires, Rev. tuberc., Paris 19:1342, 1955.

40. Warembourg and Pauchant: Essais de corticothérapie en tuberculose pulmonaire, Rev. tuberc., Paris 19:1352, 1955.

41. Lemenager, J.; Porin, J., and Bezard, J.: Action des hormones anti-inflammatoires sur certains phénomènes bronchiques chez les tuberculeux pulmonaires, Rev. tuberc., Paris 19:1357, 1955.

42. Cocchi, C.: Cortisone and Corticotropin in the Treatment of Tuberculosis in Infancy and Childhood, Am. Rev. Tuberc. 74:209, 1956.

43. Acheson, R. M.: Recent Trends in the Treatment of Primary Tuberculous Pleural Effusion, Tubercle 36:215, 1955.

44. Sors, C.; Roujeau, J.; Trocmé, Y., and Testard, R.: Indications et résultats du traitement des tuberculoses séreuses et de la tuberculose pulmonaire par l'A. C. T. H. associé aux antibiotiques, Rev. tuberc., Paris 18:522, 1954.

45. Le Tacon, J.; Poulet, J., and Fourchon, J.: Hormonotherapie de la tuberculose pleuro-pulmonaire, Rev. tuberc., Paris 19:1378, 1955.

46. Scalfi, G. F., and Rossa, G.: Cortisone Treatment During Artificial Pneumothorax, Abstract, Am. Rev. Tuberc. 73:46, 1956.

47. Harvey, A. M., and Whitehill, M. R.: Tuberculous Pericarditis, Medicine 16:45, 1937.

48. Keefer, C. S.: Tuberculosis of the Pericardium: A Study of 20 Cases, Ann. Int. Med. 10:1085, 1937.

49. Carroll, D.: Streptomycin in the Treatment of Tuberculous Pericarditis, Bull. Johns Hopkins Hosp. 88:425, 1951.

50. Wood, J. A.: Tuberculous Pericarditis: A Study of 41 Cases with Special Reference to Prognosis, Am. Heart J. 42:737, 1951.

51. Anderson, H. J.: Tuberculous Pericarditis, Brit. J. Tuberc. 48:12, 1954.

52. Falk, A., and Ebert, R. V.: Tuberculous Pericarditis Treated with Streptomycin, J. A. M. A. 145:310, 1951.

53. Shapiro, J. B., and Weiss, W.: Tuberculous Pericarditis with Effusion: The Impact of Antimicrobial Therapy, A. J. M. Sc. 225:229, 1953.

54. Goyette, E. M.; Overholt, E. L., and Rapaport, E.: The Treatment of Tuberculous Pericarditis, Circulation 9:17, 1954.

55. Clauss, R. H.: Constrictive Pericarditis Developing During Chemotherapy: Physiological Observations, in Transactions of the 15th Conference on the Chemotherapy of Tuberculosis, 1956, p. 149.

56. Bauer, H.; Robins, M.; Sachs, R., and Cummings, M. M.: Tuberculous Pericarditis Among Veterans, J. Chron. Dis. 4:559, 1956.

57. Holman, E., and Willett, F.: Treatment of Active Tuberculous Pericarditis by Pericardiectomy, J. A. M. A. 146:1, 1951.

58. Mannix, E. P., Jr., and Dennis, C.: The Surgical Treatment of Chronic Pericardial Effusion and Cardiac Tamponade, J. Thoracic Surg. 29:381, 1955.

59. Hardy, J., in discussion on Laff, H. I.; Goldberg, M., and Russell, W. F., Jr.: Bronchoscopy in Primary Tuberculosis of Childhood, Am. Rev. Tuberc. 74:267 (Pt. 2), 1956.

60. Raffel, S.: Immunopathology of Tuberculosis, Am. Rev. Tuberc. 74:60, 1956.

61. Birkhaug, K.: The Effect of Cortisone on BCG Infection in the Guinea Pig, Am. Rev. Tuberc. 69:511, 1954.

62. Chaves, A. D.; Robins, A. B.; Abeles, H.; Peizer, L. R.; Dangler, G., and Wideluck, D.: Further Observations on the Prevalence of Streptomycin and Isoniazid Resistant Strains of Mycobacterium Tuberculosis in Patients with Newly Discovered and Untreated Active Pulmonary Tuberculosis, Am. Rev. Tuberc. 74:293, 1956.

Case Reports

Idiopathic Hypoparathyroidism

WILLIAM SAPHIR, M.D., and ANTONIO CAHUÉ, M.D., Chicago

Hypoparathyroidism is most commonly encountered after thyroidectomy when the parathyroid glands are inadvertently removed or damaged. Spontaneous or idiopathic hypoparathyroidism is rare. The first case was described by Falkenheim and Beumer, in 1926.[1] Lachmann[2] collected 70 cases between 1926 and 1939. Dietrich[3] reported 113 cases in the world literature up to 1952. However, because some of these cases were not positively substantiated by records and because rigid criteria for the diagnosis were not applied, Steinberg and Waldron[4] reinvestigated the literature. They identified only 52 cases, with an additional case of their own if the following criteria were followed: (1) low serum calcium level, (2) high serum inorganic phosphorus level, (3) absence of renal insufficiency, (4) normal bones on x-rays, (5) chronic tetany. Albright[5] recognized the occurrence of a separate form of idiopathic hypoparathyroidism designated as pseudohypoparathyroidism when he found that these patients failed to respond to large doses of parathyroid hormone (Ellsworth-Howard test).[6]

The symptoms of the disease are chiefly due to hypocalcemia. Tetany with manifestations of muscular hyperexcitability, paresthesias, numbness, tingling and cramps of the extremities, laryngeal stridor, and tonic convulsions are commonly present. Other significant findings are delayed and defective dentition, cataract formation, and, particularly in children, mental retardation and epileptiformic seizures.

Submitted for publication Sept. 20, 1957.

From the Department of Medicine, Michael Reese Hospital.

The etiology of idiopathic hypoparathyroidism is unknown. Although its morbidity is high, the mortality is low. Only three autopsies are on record,[7,8] showing the parathyroids to be either absent or replaced by nonglandular tissue. In one case described by Drake et al.[9] the four parathyroid glands seen at necropsy appeared grossly normal but the parenchymal cells had been completely replaced by fat. Birth trauma, infections, and hereditary factors have been implicated. In three separate reports the disease was encountered in siblings.[10,11]

Of particular interest is the relation of idiopathic hypoparathyroidism to epilepsy. Generalized convulsions are described in 52% of the cases.[4] In some patients, grand mal convulsions are accompanied by increased spinal fluid pressure and papilledema. These findings may suggest the presence of a brain tumor.[12] Although characteristic electroencephalographic changes have been reported in this disorder,[13,14] it is not generally accepted that there are electroencephalographic changes diagnostic of hypocalcemia, but rather is the electroencephalographic pattern suggestive of epilepsy.[15] After therapy the electroencephalogram may or may not return to a normal pattern.

Taubenhaus,[16] in 1945, postulated that hypocalcemia may be a factor precipitating epileptic seizures in persons who are potential epileptics. Electroencephalographic studies have shown that a large group of the population present a typical epileptic pattern without exhibiting manifest seizures. If such a person develops hypocalcemia, epilepsy may become clinically manifest.

The following case of idiopathic hypoparathyroidism demonstrates a problem of a similar nature, namely, the absence of clinical epilepsy in the presence of both hypocalcemia and a typical epileptic electroencephalographic pattern.

Report of Case

A woman aged 57 was admitted to Michael Reese Hospital on March 31, 1956. For the preceding two months she had experienced episodes of muscular stiffness involving first the hands and arms but later her feet and legs as well. While at first these episodes were of short duration and occurred several days apart, they had become increasingly frequent, lasting for hours and appearing daily as time went on. In addition, numbness and tingling were noted in the involved parts and the patient was hardly able to move her fingers and toes during the attacks. Recently, she had also noted some shortness of breath together with a constricting sensation in her throat, at times leading to a distinct feeling of "choking." The attacks occurred at various times day or night, and no precipitating cause could be elicited. Past history revealed the presence of chickenpox in childhood and frequent headaches in later years. She had been told that the headaches were due to hypertension and had received hypotensive medication elsewhere. The family history disclosed diabetes mellitus in two brothers. Both parents had died of heart attacks.

The physical examination revealed a well-nourished rather obese patient aged 57 in no apparent distress. The blood pressure was 180/100 mm. of Hg. The eyes reacted normally to light and in accommodation. No lens opacities were noted, nor were there significant dental deficiencies. The cranial nerves were normal in function, but a strongly positive Chvostek's test was present bilaterally. The chest revealed normal respiratory expansions and full resonance with vesicular breath sounds. The heart appeared slightly enlarged, with the apex beat just outside the midclavicular line in the fifth interspace. The heart sounds were clear and distinct; the second aortic sound was somewhat accentuated, and no murmurs or thrills were noted. The abdomen was slightly distended and soft. There was no tenderness, and the liver and spleen were not palpable. Rectal and vaginal examination disclosed no significant abnormalities. The extremities were normal in regard to reflexes, motor power, sensory qualities, and peripheral circulation. However, a strongly positive Trousseau's sign was found bilaterally.

Significant laboratory tests (see Table for complete figures) were a low-grade anemia with elevation of sedimentation rate, a constantly negative urinary Sulkowitch test, and a marked hypocalcemia with hyperphosphatemia. Values on two basal metabolic tests were −6% and −8%. The electrocardiogram was interpreted as definitely abnormal because of a prolonged Q-T interval of +0.04 seconds, indicating hypocalcemia. X-rays of skull and chest showed no significant abnormalities. The electroencephalogram showed independent paroxysmal slow waves in both temporal areas, with a few small sharp spike seizure discharges.

Course.—During the first few days of hospitalization the patient exhibited mild attacks of carpopedal spasms and laryngeal stridor. Repeat serum calcium determination showed a value of 6.2 mg. 100 cc. and a phosphorus value of 7.2 mg. per 100 cc., with constantly negative Sulkowitch tests in the urine. Treatment was started with calcium lactate powder, 5 gm. t. i. d., and vitamin D, 50,000 units b. i. d. Clinical improvement was noted almost immediately, and the patient was discharged on April 7, 1956, with the Sulkowitch test showing normal calcium excretion. The Chvostek test was slightly positive, and the Trousseau test, negative. A serum calcium and phosphorus determination on May 10, 1956, showed a calcium value of 9.1 mg. per 100 cc. and a phosphorus value of 5.2 mg. per 100 cc. Subsequently, the patient

Pertinent Laboratory Data During Two Hospital Admissions

Admission	Urine	Blood Cell Count	Kahn Test	Serum Proteins	Serum Electrolytes	Others
First	Persistent negative Sulkowitch test; otherwise normal	RBC 3,800,000; Hb. 12 gm./100 cc.; WBC 7,600; differential count normal; hematocrit 35%; corpuscular index 1.0; mean corpuscular volume 92 cu.μ; sedimentation rate 40 mm. in 1 hr.	Negative	Total protein 6.7 gm./100 cc.; albumin 3.3 gm./100 cc.; total globulin 3.4 gm./100 cc.; α-globulin 1.0 gm./100 cc.; β-globulin 1.2 gm.; γ-globulin 1.2 gm.	Calcium 5.6 mg./100 cc.; phosphorus 7.2 mg./100 cc.; chlorides 102 mEq/L.; sodium 140 mEq/L.; potassium 5.48 mEq./L.; CO_2 21.9 mM./L.; BUN 19 mg./100 cc.	Bilirubin 0.8 mg./100 cc.; alkaline phosphatase 1.4 units; cholesterol 212 mg./100 cc.; esters 74%; thymol turbidity 0.8 units; thymol flocculation, zero; creatinine 1 mg./100 cc.; uric acid 4.9 mg./100 cc.; B. M. R.—6%, −8% Glucose 72 mg./100 cc.; urea N 21 mg./100 cc.
Second	Sulkowitch test positive 1+ to 2+	RBC 4,200,000 WBC 5,400; normal differential count	--	Total protein 6.3 gm./100 cc.; albumin 3.4 gm./100 cc.; globulin 2.9 gm./100 cc.	Calcium 9.2 mg./100 cc.; phosphorus 4.4 mg./100 cc.	

was observed ambulatorily by one of us (W. S.) for one year. During that time she was maintained with calcium medication and vitamin D of varying strengths, depending roughly on the amount of the calcium excretion as determined by the Sulkowitch test. The patient was readmitted to Michael Reese Hospital for evaluation on March 30, 1957. The physical findings were essentially the same as on previous admissions, with the exception that both the Trousseau and the Chvostek signs were no longer present. The electrolytes and other laboratory tests (Table) were normal.

The electrocardiogram was interpreted as normal, with no evidence of disturbed calcium balance. The electroencephalogram showed restitution to a normal pattern. The patient was discharged with a similar regimen of a somewhat reduced intake of calcium and vitamin D prescribed. She has felt well since, without recurrence of tetanic manifestations.

Comment

It has been stated that the scarcity of reported cases of idiopathic hypoparathyroidism is an indication of defective knowledge of the disease and of failure to recognize it rather than an indication that it is an extremely rare condition.[3] Indeed, the average time between onset of symptoms and establishment of diagnosis has been estimated as about eight years.[15] One patient had complained of symptoms for 31 years[4]; another, for 27 years,[15] before the underlying disorder was recognized.

Our case presented the clinical picture of hypocalcemic tetany and fulfilled the criteria of Steinberg and Waldron,[4] as stated above. If other causes of hypocalcemia, such as thyroidectomy, alkalosis, vomiting, sprue syndrome, malabsorption syndrome, and ulcerative colitis, can be excluded, the diagnosis of idiopathic hypoparathyroidism appears to be established.

Treatment with calcium and vitamin D in our case not only promptly restored the hypocalcemia with its clinical manifestations to a normal state but also reverted the previously abnormal electrocardiogram and electroencephalogram to a normal pattern.

Although a euparathyroid state can thus be maintained indefinitely, it appears clear that the basic abnormality, the parathyroid deficiency, cannot be corrected thereby. The restoration of a normal blood calcium level in hypoparathyroidism may be compared to the restoration of a normal blood sugar level in diabetes mellitus. In both conditions, symptoms are relieved and complications avoided but the basic underlying pathology continues to exist.

The relation of hypoparathyroidism to epilepsy is obscure. Idiopathic hypoparathyroidism has been misdiagnosed as grand mal epilepsy in over 50% of cases.[17] Our case exhibited no manifest seizures in spite of the combination of hypocalcemia with an abnormal electroencephalographic pattern, suggestive of epilepsy. While such a combination may readily precipitate convulsive attacks,[16] it is not necessarily so, as shown in our case.

It appears likely that additional as yet unknown factors are necessary to evolve epileptic seizures in susceptible persons. Nevertheless, the high rate of 52% of cases of idiopathic hypoparathyroidism reported to have convulsive seizures[15] strongly suggests that this disease should always be included in the etiologic considerations of epilepsy.

Summary and Conclusions

Idiopathic hypoparathyroidism is probably more prevalent than the scarcity of recorded cases seems to indicate. It can readily be recognized if a high degree of suspicion is maintained. The disease should always be considered in the differential diagnosis of epileptiformic attacks. Such attacks, however, may be absent in spite of both a hypocalcemia and a typical epileptic electroencephalic pattern.

104 S. Michigan Ave. (3).

REFERENCES

1. Falkenheim, C., and Beumer, H.: Idiopathic Tetany, Hemocrinine and Hormone of Parathyroids, München med. Wchnschr. 73:818-819 (May 14) 1926.

2. Lachmann, A.: Hypoparathyroidism in Denmark: Clinical Study, Acta med. scandinav., Supp. 121, pp. 1-269, 1941.

3. Dietrich, F. S.; Rice, M. L., Jr., and Luton, E. F.: Clinical Manifestations of Idiopathic Hypoparathyroidism: Report of One Case, Ann. Int. Med. 37:1052-1063 (Nov.) 1952.

4. Steinberg, H., and Waldron, B. R.: Idiopathic Hypoparathyroidism: Analysis of 52 Cases, Including Report of New Case, Medicine 31:133-154 (May) 1952.

5. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudo-Hypoparathyroidism: Example of "Seabright-Bantam Syndrome"; Report of 3 Cases, Endocrinology 30:922-932 (June) 1942.

6. Ellsworth, R., and Howard, J. E.: Studies on Physiology of Parathyroid Glands, Some Responses of Normal Human Kidney and Blood to Intravenous Parathyroid Extract, Bull. Johns Hopkins Hosp. 55:296-308 (Nov.) 1934.

7. Leonard, M. F.: Chronic Idiopathic Hypoparathyroidism with Superimposed Addison's Disease in Child, J. Clin. Endocrinol. 6:493-506 (July) 1946.

8. Cantarow, A.: Chronic Juvenile Hypoparathyroidism, Arch. Pediat. 49:293-304 (May) 1932.

9. Drake, T. G.; Albright, F.; Bauer, W., and Castleman, B.: Chronic Idiopathic Hypoparathyroidism: Report of Six Cases with Autopsy Findings in One, Ann. Int. Med. 12:1751-1765 (May) 1939.

10. Camp, J. D.: Symmetrical Calcification of the Cerebral Basal Ganglia, Radiology 49:568-577 (Nov.) 1947.

11. Sutphin, N.; Albright, F., and McCune, D.: Five Cases (Three in Siblings) of Idiopathic Hypoparathyroid Associated with Moniliasis, J. Clin. Endocrinol. 3:625-634 (Dec.) 1943.

12. Berezin, S. W., and Stein, J. D.: Idiopathic Hypoparathyroidism: Case Simulating Epilepsy and Brain Tumor, J. Pediat. 33:346-351 (Sept.) 1948.

13. Odoriz, J. B.; del Castello, E. B.; Manfredi, J. F., and de la Balze, F. A.: Parathyroid Insufficiency and the Human Electroencephalogram, J. Clin. Endocrinol. 4:493-499 (Oct.) 1944.

14. Gotta, H., and Odoriz, J. B.: Electroencephalogram in Hypoparathyroidism with Tetany and Epilepsy, J. Clin. Endocrinol. 8:674-686 (Aug.) 1948.

15. Van Ommen, R. A.: Clinical Manisfestations of Idiopathic Hypoparathyroidism: Report of a Case, Cleveland Clin. Quart. 21:72-78 (April) 1954.

16. Taubenhaus, M., and Engle, H. M.: Clinical Observations on Case of Idiopathic Tetany and Epilepsy, J. Clin. Endocrinol. 5:147-150 (March) 1945.

17. Jernigan, J. A., and Sadusk, J. F., Jr.: Idiopathic Hypoparathyroidism: Discussion and Presentation of Case, Stanford M. Bull. 11:266-271 (Nov.) 1953.

Pericardial Biopsy with Vim-Silverman Needle

L. M. SANGHVI, M.R.C.P. (London), D.T.M.&H. (England), and K. C. SAMUEL, M.D., Jaipur, India

Etiologic diagnosis of pericarditis with effusion, particularly the differentiation of the tuberculous from the nonspecific type, has become extremely important since the introduction of chemotherapeutic and antibiotic agents. Though uncomplicated primary tuberculous pericarditis is rare, the infection at the onset frequently involves only the pericardium, while other manifestations occur later during the course of the illness. Again, the onset of the disease may be acute and closely resemble the acute nonspecific type, and if the correct diagnosis is delayed the prognosis may be greatly affected. Laboratory studies involve expense of valuable time and may yet be inconclusive in some cases. In several such cases, a pericardial biopsy through an anterior thoracotomy has established a specific diagnosis.[1-5] The purpose of this paper is to describe a simple method of pericardial biopsy with the Vim-Silverman needle.

Technique

The biopsy site is selected, after fluoroscopic examination of the chest, in the fifth interspace about 2 cm. inside the left border of the cardiac dullness and about the same distance lateral to the apical impulse if it is distinct. After premedication with morphine and atropine and with the patient in the sitting position, the biopsy site down to the pericardium is anesthetized with 2% procaine. A small skin incision is made, and a diagnostic aspiration with an 18 gauge needle is first done with a view to determine that the enlargement of the cardiac dullness and shadow is due to effusion and not to cardiac dilatation, which sometimes occurs in nonspecific pericarditis; that the distance between the parietal and the visceral pericardium is not less than 0.5 cm., and the exact distance at which the fluid is encountered. This distance is measured on the biopsy needle, from the tip of the inserted biopsy shaft, and a Kelly clamp is applied. The biopsy needle with the obturator in place is then slowly advanced through the skin incision up to this distance. The obturator and the Kelly clamp is removed; the biopsy shaft is inserted, and the outer needle advanced forward about 1.8 cm. (or the distance from the tip of the biopsy shaft to that of the outer needle). Both the needle and the shaft are rotated through 360 degrees and withdrawn together, and the skin is closed with one nonabsorbable (silk) suture. The shaft contains the sample of tissue.

Submitted for publication Sept. 23, 1957.

From the Departments of Cardiology and Pathology, Sawai Man Singh Hospital and Medical College. Additional Professor in Medicine (Dr. Sanghvi) and Lecturer in Pathology (Dr. Samuel).

Report of Cases

CASE 1.—A 20-year-old youth was admitted on Feb. 6, 1957, complaining of cough and fever of three weeks' duration, dyspnea and dull precordial ache of seven days' duration, and edema of the feet of four days' duration. Physical examination revealed a well-built well-nourished man in great distress due to orthopnea. There was cyanosis, marked engorgement of the neck veins, ascites, and 2+ edema of the feet. The pulse was paradoxical and irregular, with a rate of 130 per minute, while the heart rate was 160; the temperature, 100 F, and the blood pressure, 95/80 mm. of Hg. The liver was enlarged 4 in. below the costal margin and tender. The area of cardiac dullness was considerably enlarged, and the heart sounds were normal, but a pericardial friction rub was audible at the base. There were signs of pleural effusion at the right lung base.

Laboratory examination revealed a total leukocyte count of 9400 per cubic millimeter, with 90% neutrophils and 10% lymphocytes; an elevated E. S. R. of 45 mm. in one hour (Westergren); hemoglobin, 11 gm. per 100 cc.; venous pressure, 19 cm., and arm-to-tongue circulation time, 25 seconds. The P. P. D. tests with first and second strength were negative. The chest x-ray showed considerable enlargement of the cardiac shadow, suggestive of pericardial effusion, and pleural effusion on the right side. The electrocardiogram showed atrial fibrillation, with an average ventricular rate of 160 per minute and inversion of T waves in Leads I, aV_L, and V_{4-6} and flattening in Leads III and aV_F. On Feb. 10, the rhythm

Fig. 1 (Case 1).—Roentgenogram of the chest on March 3.

was regular and there was progressive inversion of T waves consistent with pericarditis. On Feb. 7, hemorrhagic fluid, 1020 and 500 cc., was aspirated from the right pleural and the pericardial cavity, respectively. No organisms were seen either on smear or on culture.

Acute nonspecific pericarditis with congestive failure was suspected because of the acute onset and rapidly increasing severity of the illness, absence of any evidence of a tuberculous lesion elsewhere in the body, and the negative P. P. D. test.

The patient was given a salt-poor diet and treated with acetylsalicylic acid and digoxin orally and injections of a mercury preparation (Neptal) intramuscularly. There was rapid improvement, and on Feb. 10 sinus rhythm was restored. By Feb. 14, the patient was afebrile and had lost 14 lb. of weight; there was no dyspnea or edema; the liver was palpable only 1 in. below the costal margin; the cardiac shadow was smaller; there was no pleural effusion, and the venous pressure had decreased to 14 cm. and the circulation time to 13 seconds.

A week later, however, there was recurrence of pyrexia and on March 3, the venous pressure had risen to 23 cm., though the circulation time was 11 seconds; the E. S. R. was 75 mm. in one hour, and the cardiac shadow was still considerably enlarged (Fig. 1). At this stage a pericardial biopsy was done with the Vim-Silverman needle and 420 cc. of fluid was aspirated. The fluid was sent for culture and guinea pig inoculation. Histological examination of the biopsy material revealed connective tissue with Langhans type of giant cells, suggestive of tuberculous pericarditis, though acid-fast bacilli could not be demonstrated (Fig. 2). Later, necropsy of the inoculated guinea pig, on April 12, demonstrated tuberculous lesions with acid-fast bacilli and confirmed the diagnosis. A second P. P. D. test was also positive.

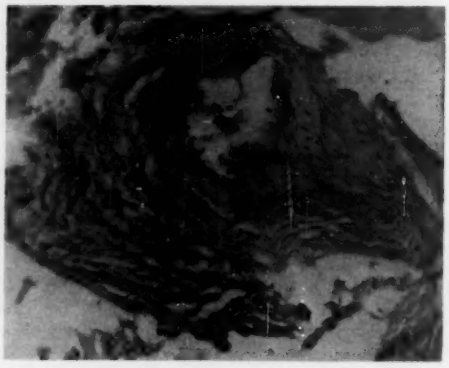
The patient was treated with isoniazid, 300 mg., and streptomycin, 1 gm., daily. He became afebrile within a fortnight. At the time of discharge from the hospital, on Aug. 6, 1957, he was relieved symptomatically and the E. S. R. was 10 mm. in one hour, though the venous pressure was still elevated to 19 cm. He was advised to continue the treatment.

Case 2.—A 19-year-old youth was admitted on Feb. 11, 1957, complaining of dry cough, dyspnea on exertion, and pain in the epigastrium of 3 months' duration, and swelling of the abdomen and edema of the feet of 15 days' duration. Two months prior to this illnes he had malarial fever for one month, but there had been no fever during the present illness.

Physical examination revealed a well-built well-nourished man, with dyspnea on slight exertion, slightly engorged neck veins, 1+ edema of the feet, liver enlarged 2 in. below the costal margin, and a palpable spleen. The pulse was paradoxical, with a rate of 110 per minute, and the blood pressure was 112/88 mm. of Hg. The heart sounds were faint, and there was no murmur or pericardial friction rub. There were signs of pleural effusion on the right side.

Laboratory examination revealed a total leukocyte count of 7500 per cubic millimeter, with 65% neutrophils, 30% lymphocytes, and 5% mononuclear cells; hemoglobin, 14 gm. per 100 cc.; E. S. R., 4 mm. in one hour (Westergren); negative Kahn and Paul Bunnell tests; venous pressure, 15 cm., and arm-to-tongue circulation time, 13 seconds. L. E.-cell phenomenon could not be demonstrated, and the P. P. D. test was negative.

Fig. 2 (Case 1).—An area of the parietal pericardium, showing connective tissue with cellular infiltration and a Langhans type of multinucleated giant cell suggestive of chronic tuberculous inflammation.



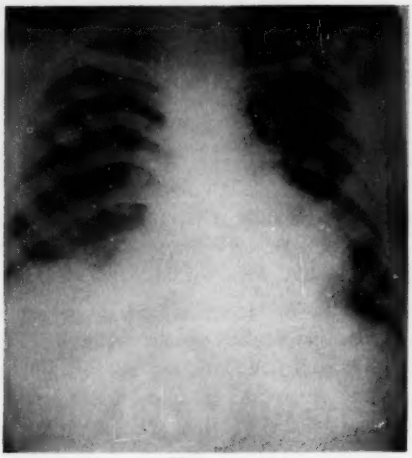


Figure 3

Fig. 3 (Case 2).—Roentgenogram of the chest on March 20.

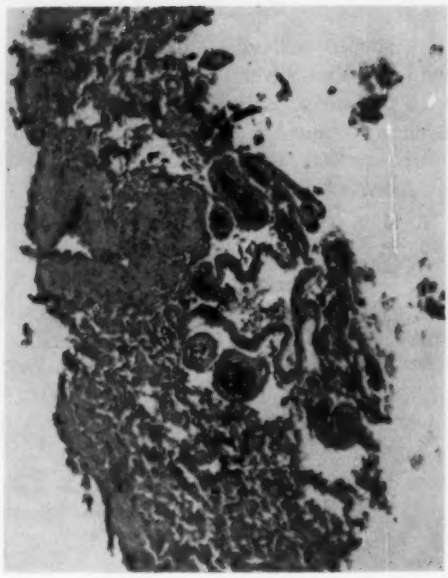


Figure 4

Fig. 4 (Case 2).—Granulation tissue with endothelial lining and numerous adult type of blood vessels suggestive of chronic inflammation of a nonspecific nature.

The chest x-ray showed considerable enlargement of the cardiac shadow and pleural effusion on the right side. The electrocardiogram showed low voltage of QRS complexes and T changes consistent with pericarditis. Clear straw-colored fluid, 150 cc., could be drawn out on pericardial tap, and 1400 cc., from the right pleural cavity. No organisms or acid-fast bacilli could be demonstrated either on smear or on culture in any of the fluids.

A specific etiology of the chronic pericarditis could not be established. Absence of pyrexia, normal E. S. R., negative P. P. D. test, and absence of a tuberculous focus elsewhere were against, while a chronic illness with a gradual onset and absence of chest pain and of friction sounds favored, a tuberculous etiology. The patient felt better with a salt-poor diet and injections of mercurial diuretics, and a chest x-ray on March 20 showed no pleural effusion but the cardiac shadow was still enlarged (Fig. 3). A pericardial biopsy was now done, and the material on histological examination revealed granulation tissue with adult type of blood vessels suggestive of a chronic nonspecific lesion (Fig. 4).

During his stay in the hospital for a period of three months the patient had no pyrexia, and his E. S. R. was normal and culture of the pericardial fluid was negative for acid-fast bacilli on repeated examinations. A second P. P. D. test was negative, and no evidence of tuberculosis could be found in guinea pigs inoculated with several samples of aspirated pericardial fluid. He had symptomatic relief, and the cardiac shadow became smaller, but the venous pressure and liver enlargement gradually increased, suggesting development of constrictive pericarditis. He refused operation and left the hospital on May 20.

Comment

The method of pericardial biopsy described here is simple and painless. There were no complications, and the material obtained in each of the two cases gave the desired information. In the first case the tuberculous etiology shown by the biopsy tissue was confirmed later by the guinea pig inoculation report, the change from negative to positive of the P. P. D. test, and the clinical improvement after specific therapy. In the second case the histological diagnosis of chronic nonspecific pericarditis appeared to be confirmed by his further clinical course and repeatedly negative laboratory studies. The method is considered suitable in cases with effusion which, however, is not minimal and particularly in those with much thickening of the parietal pericardium.

Summary

A simple method of pericardial biopsy with the Vim-Silverman needle in patients with pericardial effusion is described. The material obtained from each of the two patients was sufficient to establish the etiologic diagnosis of pericarditis.

S. M. S. Hospital & Medical College, Department of Medicine, 10, Vivekanand Rd.

REFERENCES

1. Janovsky, R. C.; Boettner, J. F.; Vanordstrand, H. S., and Effler, D. B.: Recurrent Tuberculous Pericarditis, Ann. Int. Med. 37:1268, 1952.

2. Groves, L. K., and Effler, D. B.: Primary Chylopericardium, New England J. Med. 250:520, 1954.

3. Williams, C., and Soutter, L.: Pericardial Tamponade: Diagnosis and Treatment, A. M. A. Arch. Int. Med. 94:571, 1954; Correction 94:865, 1954.

4. Barr, J. F.: The Use of Pericardial Biopsy in Establishing Etiologic Diagnosis in Acute Pericarditis, A. M. A. Arch. Int. Med. 96:693, 1955.

5. Proudfit, W. L., and Effler, D. B.: Diagnosis and Treatment of Chronic Pericarditis by Pericardial Biopsy, J. A. M. A. 161:188, 1956.

Treatment in Internal Medicine

The Treatment of Schistosomiasis

R. S. DÍAZ-RIVERA, M.D.; F. RAMOS-MORALES, M.D.; Z. R. SOTOMAYOR, M.D., and SYLVIA SANTIAGO, M.D., San Juan, P. R.

The proper evaluation of the effectiveness of therapy in schistosomiasis is rendered difficult by the protean clinical manifestations of the disease, the invariable tendency toward chronicity, and the lack of accurate information pertaining to the natural course of the disease. From the outset a pessimistic attitude is assumed in view of the failure to discover drugs of definite efficacy. A review of the voluminous medical literature dealing with this subject fails to reveal a single medication that can effectively control the ravages of the disease. Thus, after maturation of the parasite and oviposition, progressive, and at times irreversible, tissue changes occur, emphasizing the early recognition of the disease as the most important governing factor in the determination of the degree of possible therapeutic success in the future. However, it appears as if the direct contact of the adult parasites and their eggs with the host's tissues leads to pathological alterations which at present may remain unaltered or, perhaps, only abbreviated by early treatment and that organization with cicatrization, at times intense and generally detrimental, is the only possible body defense.[1,2] The prevention of these pathological alterations governed by vascular damage, obstructive vascular phenomena, and actual destruction of tissues from the direct effect of the adult parasites and their eggs may be attained only through the actual destruction of the parasite.[3-15] The experience of others and our own emphasize the limitations of most of the therapeutic agents in common use.

The earliest stages of schistosomiasis are generally dominated by a hypersensitivity state, with the parasite and ova as the sources of allergens. The severity of the process appears to be mainly governed by the infecting dose and the general condition of the host. From the outset the symptoms and signs may point to a severe systemic disease with chills and fever; gastrointestinal manifestations (diarrhea, nausea, vomiting, abdominal pain, and splenic and hepatic enlargement); cutaneous allergic manifestations, with hypereosinophilia, and, frequently, pulmonary alterations indistinguishable from a pneumonic consolidation accompanied by wheezing respiration. It seems as if the duration of this acute stage depends on the adequacy of the immunological responses, since the administration of antimonials in heavy doses fails to alter its course.[1,2,16-19]

Submitted for publication Jan. 15, 1958.

This work was supported in part by the Parke, Davis & Company Research Fund and Contract No. DA-49-007-MD-649, Office of the Surgeon General, Department of the Army, Washington, D. C.

From the Departments of Medicine of the University of Puerto Rico School of Medicine and the San Juan City Hospital. Professor and Head of the Department of Medicine of the University of Puerto Rico School of Medicine and the San Juan City Hospital (Dr. R. S. Díaz-Rivera); Assistant Professor of Medicine of the University of Puerto Rico School of Medicine and Assistant Attending and Chief of the Section of Infectious Diseases of the San Juan City Hospital (Dr. F. Ramos-Morales); Associate in Medicine of the the University of Puerto Rico School of Medicine and the San Juan City Hospital (Dr. Z. R. Sotomayor); Research Fellow of the Department of Medicine of the University of Puerto Rico School of Medicine (Dr. Sylvia Santiago).

In other instances, the disease may be mistaken for a less distinctive gastrointestinal or urinary tract disorder, and the diagnosis awaits the manifestations of progressive pathologic alterations in the intestines and liver (Schistosoma mansoni and S. japonicum) or in the urinary bladder and liver (S. hematobium). Thus, the physician in nonendemic areas is mainly concerned with the chronic form of the disease, at times accompanied by advanced pathologic alterations pointing to fragile esophageal varices from portal hypertension or extensive pathology in the urinary bladder and ureters. Although pathologic pulmonary alterations are generally present, pulmonary hypertension with chronic cor pulmonale is rather uncommon. In most instances the physician will be consulted for indefinite symptoms related to a vague chronic gastrointestinal or urinary tract disorder, and the great bulk of cases of schistosomiasis will be discovered accidentally during a routine stool or urine analysis. Many of these may be asymptomatic while harboring parasites continuously laying eggs, the minority of which extrude through the intestine or bladder to appear in the dejecta. Living eggs in the dejecta, in the rectal and urinary bladder mucosa, or in the liver constitute undeniable proof of an active infection. Further studies may reveal the ravages of advanced schistosomiasis in the asymptomatic group, but in most instances the stigmata of the disease are less evident or will remain undiscovered.[20-22]

The drugs in common use are contraindicated in the management of the more advanced vascular complications of schistosomiasis. Surgical procedures have been devised for the correction of portal hypertension with fragile esophageal varices (portocaval anastomosis) and for hypersplenism (splenectomy with or without portocaval anastomosis). Advanced ureteral obstruction with hydronephrosis is best managed by mechanical means.[20] There is no adequate therapy for chronic cor pulmonale due to obstructive pulmonary arteriolar disease or for the syndrome of multiple pulmonary arteriovenous shunts with intense cyanosis, rarely observed in the disease.[23]

Before analyzing the therapeutic approach of schistosomiasis, it must be emphasized that it is consensus of opinion that the manifestations of the disease may be more an index of the socioeconomic status than of the parasitosis per se.[2,24] A good dietary regimen and the improvement of the living conditions are perhaps important factors in the prevention of the most serious infections and complications. However, if it is accepted that progressive damage may result from continuous oviposition, it can be concluded that all patients with living eggs in the dejecta, or in tissues, should receive treatment. As stated previously, a pessimistic attitude is assumed as to efficacy of the available drugs and the lack of adequate criteria for cure.

It is justifiable to assume that the main achievement of therapy at present is most often a transitory suppression of oviposition and, in some instances, permanent sterility of the worms. This, of course, is neither an adequate nor desirable criterion for cure, since there are no accurate methods to determine the deposition of eggs in the viscera. Only those eggs extruding into the intestine or urinary bladder are seen in the dejecta. The extensive egg deposition in the liver and other organs in preference to extrusion into the intestinal canal is perhaps the greatest drawback in the determination of curability. Furthermore, even in the absence of viable eggs in the dejecta, the mucosa of the urinary bladder and intestine, or the liver, it remains to be proven whether the permanent paralysis of oviposition resulted from treatment or from the adequacy of the defensive mechanisms of the host. There is experimental and clinical proof to suggest the development of protection against one or more infections under certain conditions.[25]

The therapeutic approach to schistosomiasis was initiated with the discovery

of the parasite in 1851; however, it was not until 1913 that favorable results with emetine hydrochloride started to appear in the literature. The early stimulating reports were soon blemished by the toxic effects of this drug, including, among others, toxic myocarditis; peripheral neuritis; hepatitis; myositis; generalized urticaria and purpuric skin lesions; nausea, vomiting, and diarrhea; easy fatigability, and listlessness, as well as other sensory disturbances. Even if this drug may effectively paralyze oviposition, the signs of toxicity in 30% to 90% of cases render its general use impractical and dangerous.[21,22,26]

In 1918, antimony potassium tartrate (tartar emetic) was heralded as efficacious in the management of S. mansoni and S. hematobium infections, and its introduction led to experimentation with most of the antischistosomal agents used now.[27] Antimony potassium tartrate is regarded as the most potent of all the trivalent antimonials, but it frequently produces violent toxic reactions (nausea, vomiting, dizziness, epigastric pain, diarrhea, myalgia, pneumonia with wheezing respiration, toxic myocarditis, headache, fainting, facial edema, hepatitis, vascular collapse, and even death); the intravenous administration frequently accompanied by phlebitis is a drawback in field studies, and it is chemically unstable, limiting its use to the most favorable conditions.[28-30]

For the sake of clarity some of the methods of administration of this drug will be summarized. In 1945, the intensive method of treatment was devised to facilitate mass therapy in endemic areas.[31] A total dose of 12 mg. per kilogram of body weight was given in six equal injections thrice a day for two successive days. Claims of a 100% cure rate were made on the basis of the results obtained in 100 patients.[32] However, the period of study and the criteria for cure (absence of living eggs in the dejecta) lends validity to the results. The work was repeated in 1948 under more controlled conditions, and serious immediate reactions including electrocardiographic abnormalities were recorded. With use of the same criteria there was a 67% cure rate, and the authors considered the method as "too drastic." To ameliorate the undesirable toxic reactions, the six doses recommended originally for two days were given in a period of six successive days. While the cure rate remained unchanged, the side-reactions were less frequent and milder. In 1948, an attempt was made to devise a method of rapid therapy with reasonable safety to the patient. A dose of 18 mg. per kilogram of body weight divided into six equal daily injections was given to 8 patients; 24 mg. per kilogram over a period of 10 days, to 4, and 15 mg. per kilogram divided in six equal daily injections, to 28. There was a 67.8% cure rate on the basis of a one-month follow-up, and 12 to 15 mg. of antimony potassium tartrate per kilogram of body weight administered in six days was adopted as the safest method for rapid therapy in Africa.[33]

Most[28,34] has suggested that total doses of 2.5 gm., 1.8 gm., and 1.5 to 1.75 gm. of antimony potassium tartrate will cure 90% of infections with S. japonicum, S. mansoni, and S. hematobium infections, respectively. The courses of therapy are prolonged, but they yield a margin of safety, despite the drawback of toxicity. The results obtained from the use of antimony potassium tartrate in total doses over 1.8 gm. or more in S. japonicum infections were apparently excellent. It must be emphasized that the drug must be given in increasing intravenous daily doses from 8 cc. of a 0.5% solution to 30 cc. or more, a tedious procedure which may extend for 29 days or longer, generally attended by complications requiring constant medical supervision.

In 1930, reports started to appear in the medical literature on the use of stibophen (Fuadin) in the treatment of S. mansoni and S. hematobium infections.[35] Like sodium antimony tartrate, this is a trivalent antimonial, but it is less toxic and more stable, and it can be given intramuscularly

with little local irritation. Several attempts at proper evaluation of the effectiveness of this drug have appeared in the literature.[29,36-40]

Experience has demonstrated that the classical use of a total dose of 40 to 50 cc. of 6.3% solution of the drug divided in 9 or 10 intramuscular injections is generally inadequate in the management of the disease. There is little information pertaining to its effects in the early phases of schistosomiasis. Very few prolonged well-controlled follow-up studies have appeared in the literature, and the problem of the differentiation of true relapses from reinfections introduces some unreliability to the interpretation of the results obtained.

Intensive therapy with stibophen has been tried by several investigators in S. hematobium infections with poor results.[41-43] In a series of 55 cases, adults received a total of 34 cc. and children, 17 cc. in three days. Considering that 1 cc. of a 6.3% solution of the drug contains 8.5 mg. of trivalent antimony, these patients received 21.5 and 10.7 mg., respectively. A short follow-up revealed 40% to 50% of failures. The side-effects were rather mild, but there was "brisk" hematuria in 17 patients.[44]

The drug appears to be of only limited benefit in total doses of 40 to 100 cc. (340 to 850 mg. of trivalent antimony) if given intramuscularly in doses of 5 cc. on alternate days.[1,28,34] Repeated treatments by the same method with 40 to 60 cc. have failed to alter the progressive pathological alterations, and in only a few instances do they transitorily paralyze oviposition. Single treatments with 75 to 100 cc. of the drug generally suppress oviposition within 13 to 33 days but do not alter the clinical course of the disease. Paralysis of oviposition may persist for as long as five months to one year in children after initial total doses of 60 to 100 cc. Smaller total doses of 40 to 60 cc. invariably failed to suppress oviposition in heavily infected children.[1]

Whether larger total doses given in 5 cc. daily intramuscular injections would effect cure remains to be determined. The side-reactions are at times as intense as those observed with antimony potassium tartrate.[38,45-51] Perhaps, smaller daily doses for longer intervals may be beneficial in paralyzing oviposition, in shortening the life of the parasite, or in its eradication. However, clinical data on this method are lacking.

Although the pentavalent antimonials, ethylstibamine (Neostibosan) and stibamine (Neostam), have been tried with greater success in the experimental animal, the results of clinical trials are not convincing. The proper evaluation of the effectiveness of other antimonials is awaited with expectation in view of the high incidence and, at times, the intense morbidity of the disease. This is substantiated by the results from adequately controlled experimental studies indicating that doses of stibophen or antimony potassium tartrate tolerable to man are inadequate in the suppression of the infection in lower animals. Thus, it has been demonstrated that only with daily doses of 4 mg. of stibophen for 12 consecutive days can a 20 gm. mouse be freed of the disease, while 2 mg. daily doses for the same period invariably ended in failure. If these results applied to man, it would represent the administration of a daily dose of 12 gm. of stibophen for 12 days (total 144 gm.) to effect cure in a 60 kg. man. It has also been shown that heavy doses of antimony potassium tartrate are ineffective in the eradication of the infection in mice.[52-54]

The group of compounds known as the Miracils was first synthesized in Germany and studied for nearly a decade as potential chemotherapeutic agents for schistosomiasis mainly in Africa and South America. Miracil D, the best known of these compounds, is the hydrochloride of 1-methyl-4-β-diethylaminoethylaminothiozanthone, which appears to act primarily against the adult forms of S. hematobium and S. mansoni and is apparently ineffective against S. japonicum infections. It appears as if the drug is capable of suppressing oviposition by interfering with the reproductive function of the parasites. The drug is

readily absorbed from the gastrointestinal tract and presumably degraded by the liver, and only 10% of the ingested amount appears in the urine. It is generally administered at 12-hour interval in enteric-coated tablets in daily doses of 10 mg. per kilogram of body weight for 12 days.[55] A total dose of 136 mg. per kilogram given in divided doses for seven days ended in relapse within six months in the majority of instances.[56] The administration of 60 mg. per kilogram has led to a high cure rate in Rhodesia, where it is claimed that the disease is less severe and the chances of infection less probable than in Egypt. The administration of three courses of two daily 1 gm. doses to 13 prisoners for three days led to cure in 10 and failure in 3 within six months of follow-up. Four heavily infected patients who received three courses of Miracil A responded favorably with the same doses as for Miracil D; however, complete failure was recorded in three of four patients with milder infections after two courses of the drug.[57]

The Miracils need further clinical investigation, since an effective drug for oral use is urgently needed in the management of schistosomiasis. This would represent a great advance in the therapy of the disease. However, the toxic manifestations are numerous and, at times, severe: abdominal pain, nausea, vomiting, vertigo, tremors, restlessness, insomnia, headache, and nerve deafness.

The results in man have been confirmed in the experimental animal, where significant decreases in the parasite counts were recorded in S. mansoni infection.[52,53] The beneficial effects of Miracil D seem to compare favorably with those of antimonials. Death is generally preceded by convulsions in experimental animals given heavy doses of the drug, and chronic intoxication is usually accompanied by hepatic and renal damage.[55]

Comment

The parasiticidal effects of some of the antimonial drugs have been confirmed in most of the experimental animals susceptible to infection with the Schistosoma. Transitory or prolonged and partial or complete suppression of oviposition occurs in the infected man and laboratory animal receiving nontoxic doses of antimony potassium tartrate and stibophen, through their interference with the function of the reproductive system of the parasite. However, the adequate early response as evidenced by cessation of oviposition, measured by the absence of eggs from the dejecta or surgically approachable areas of the body, should not be used as a criterion for cure. The experimental evidence suggests that the antimonials promote a migration of the unmated parasites to the hepatic venous radicles. Observations made a few weeks after the administration of heavy doses of these drugs to infected mice have led some investigators to conclude that the effects on the parasite are rather transitory. The parasites descend to the mesenteries, where pairing, copulation, and reassumption of oviposition occurs, with egg extrusion into the intestinal canal and their reappearance in the feces. Thus, generally the effects of antimonials are repressive rather than curative. The total eradication of the infection would require amounts not easily tolerated by either man or the experimental animal. It must be emphasized that perhaps newer methods may be devised by which cure may be attained without much danger to the host.

It has been claimed that heavy doses of antimonials are curative; but in most studies the period of observation has been limited, and in some instances, it is inferred that relapses of the disease have been interpreted as reinfections. Inasmuch as the smallest percentage of eggs deposited by the female worm passes in the feces and/or urine, it is justifiable to believe that ova may be continuously carried to the viscera in the absence of extrusion. With the inadequate clinical methods at our disposal it belongs to the pathologist to determine curability by either demonstrating living eggs in the tissues or by producing the parasites. Thus, the practicing physician is at a loss to ascer-

tain curability by the methods in common use. Furthermore, granting that the parasites are destroyed, with the consequent cessation of egg production, it remains to be determined whether the already deposited eggs will not perpetuate the pathological alterations.

Since the disease may not be effectively controlled by the drugs available at present, resistance and immunity assume an importance worthy of discussion. There is presumptive evidence in support of human resistance or immunity to schistosomiasis as evidenced by the decrease in intensity and frequency of infection with age. This has led some investigators to think of the possibility of a mechanism leading to increased tolerance to the infection or to an actual restraint in the advancement of the disease in middle-aged and older people irrespective of therapy. It has been suggested that heavy and repeated infections may lead to resistance or immunity, while lighter and perhaps infrequent infections, though of great importance to the host, produce only sufficient resistance to limit the disease process to the extent that is observed in children, half of them remaining infected for indefinite periods.

True immunity has been demonstrated by Fisher in S. intercalatum infections.[58] Newsome [25] has suggested that no definite resistance develops in man until full maturation is attained by S. mansoni. He suggests the possibility of the production of a cercaricidal substance in the host's serum to account for the increasing resistance. As suggested by other authors, an adequately resistant host may be able to eradicate the first infection before maturity of the parasite and is even more efficiently protected against subsequent infections. The work of Vogel and Minning [59] indicates that a poor host would permit the initial infection to mature but may be spontaneously dewormed after a few months through the development of immunity. If the initial infections are light, reinfections may occur with full maturation of the parasite, but the progression of the disease may not be severe if the reinfections are light, indicating that low titers of antigen will not lead to strong immunological responses. In some instances, permanent immunity may persist in the absence of the adult parasite and their eggs either spontaneously or as a result of therapy.

Summary

We have attempted to analyze the rather unrewarding present-day methods of therapy in schistosomiasis with an objective and unprejudiced approach. Inasmuch as the criteria for cure are not well established and our knowledge of the life history of the disease is limited, definite conclusions as to the best method of treatment of the disease are unwarranted. Further therapeutic developments, results of more immunological studies, and analyses of large series of cases with proper follow-up are awaited with expectation for the solution of this extremely important medical problem.

University of Puerto Rico School of Medicine, School of Tropical Medicine (22).

REFERENCES

1. Díaz-Rivera, R. S.; Ramos-Morales, F.; Koppisch, E.; Garcia-Palmieri, M. R.; Cintrón-Rivera, A. A.; Marchand, E. J.; González, O., and Torregrosa, M. V.: Acute Manson's Schistosomiasis, Am. J. Med. 21:918, 1956.

2. Díaz-Rivera, R. S.; Ramos-Morales, F.; Sotomayor, Z. R.; Lichtenberg, F.; García-Palmieri, M. R.; Cintrón-Rivera, A. A., and Marchand, E. J.: The Pathogenesis of Manson's Schistosomiasis, Ann. Int. Med. 47:1082, 1957.

3. Meleney, H.; Sandground, J.; Moore, D.; Most, H., and Carney, B.: The Histopathology of Experimental Schistosomiasis: II. Bisexual Infections with S. Mansoni, S. Japonicum and S. Hematobium, Am. J. Trop. Med. 2:883, 1953.

4. Koppisch, E.: Studies on Schistosomiasis Mansoni in Puerto Rico: IV. The Pathological Anatomy of Experimental Schistosomiasis Mansoni in the Rabbit and Albino Rat, Puerto Rico J. Pub. Health & Trop. Med. 13:1, 1937.

5. Yolles, T.; Moore, D., and Meleney, H.: Postcercarial Development of Schistosoma Mansoni in the Rabbit and Hamster After Intraperitoneal and Percutaneous Infection, J. Parasitol. 35:276, 1949.

6. Fairley, N. H.: A Comparative Study of Experimental Bilharziasis in Monkeys Contrasted with the Hitherto Described Lesions in Man, J. Path. & Bact. 23:289, 1919.

7. Koppisch, E.: Studies on Schistosomiasis Mansoni in Puerto Rico: VI. Morbid Anatomy of the Disease as Found in Puerto Ricans, Puerto Rico J. Pub. Health & Trop. Med. 16:396, 1941.

8. Koppisch, E.: Anderson's Text Book of Pathology, St. Louis, C. V. Mosby Company, 1948.

9. Fairley, N. H.: Studies in the Chemotherapy and Immunity Reactions of Schistosomiasis, Tr. Roy. Soc. Trop. Med. & Hyg. 20:236, 1926.

10. Hoeppli, R.: Histological Observations in Experimental Schistosomiasis Japonica, Chinese M. J. 46:1169, 1932.

11. Bang, F. B., and Hawston, N. G.: Studies on Schistosomiasis Japonica: IV. Chemotherapy of Experimental Schistosomiasis Japonica, Am. J. Hyg. 44:348, 1946.

12. Giovannola, A.: Specific Action of Some Drugs on Experimental Infections with Schistosoma Mansoni, Am. J. Hyg. 24:102, 1946.

13. Lee, C. U.: Treatment of Schistosomiasis Japonica with Fouadin in Experimentally Infected Rabbits, Chinese M. J. 46:1179, 1932.

14. Khaw, O. K.: Concentrated Fouadin in Treatment of Schistosomiasis Japonica in Rabbits, Proc. Soc. Exper. Biol. & Med. 32:520, 1934.

15. Pons, J. A., and Hoffman, W. A.: Febrile Phenomena in Schistosomiasis Mansoni in Puerto Rico: V. Clinical Aspects of Schistosomiasis in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. 13:171, 1937.

16. Miller, M. J., and Lyon, H.: Treatment of Vesical Schistosomiasis with Stibophen, Am. J. Trop. Med. 4:1049, 1955.

17. Pifano, F., and Mayer, M.: Sobre el comportamiento de la reacción de Fairley en los estados clínicos de la esquistosomiasis mansoni, Rev. san. y asist. social 7:379, 1942.

18. Ritchken, J., and Gelfand, M.: Katayama Disease, Early Toxaemic Stage of Bilharziasis, Brit. M. J. 1:1419, 1954.

19. Ritchken, J.: Bilharzial Fever, Cent. African J. Med. 1:37, 1955.

20. Gelfand, M.: The Diagnosis and Prognosis of Schistosomiasis, Am. J. Trop. Med. 29:945, 1949.

21. Strong, R. P.: Stitt's Diagnosis and Treatment of Tropical Diseases, Ed. 7, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1954.

22. Manson-Bahr, P. H.: Manson's Tropical Diseases, Ed. 14, Baltimore, Williams & Wilkins Company, 1954.

23. Marchand, E. J.; Marcial-Rojas, R. A.; Rodríguez, R.; Polanco, G., and Díaz-Rivera, R. S.: The Pulmonary Obstruction Syndrome in Schistosoma Mansoni Pulmonary Endarteritis: Report of 5 Cases, A. M. A. Arch. Int. Med. 100: 965, 1957.

24. Chandler, A. S.: Introduction to Parasitology, New York, John Wiley & Sons, Inc., 1955.

25. Newsome, J.: Problems of Fluke Immunity with Special Reference to Schistosomiasis, Tr. Roy. Soc. Trop. Med. & Hyg. 50:258, 1956.

26. Peltier, M., and Raynal, J.: Le Chlorhydrate d'émétine en injections sous-cutanées dans le traitetment des bilharzioses vésicales et intestinales, Bull. Soc. path. exot. 22:168, 1929.

27. Christopherson, J. B.: The Successful Use of Antimony in Bilharziasis, Lancet 2:325, 1918.

28. Most, H.: Treatment of Schistosomiasis, Am. J. Trop. Med. 4:455, 1955.

29. Spingarn, C. L., and Edelman, M. H.: Observations on the Treatment of Schistosomiasis Mansoni with Fuadin, Ann. Int. Med. 42:1198, 1955.

30. Lashbrey, F. O., and Coleman, R. B.: Notes on 1000 Cases of Bilharziasis Treated with Antimony Tartrate, Brit. M. J. 1:229, 1921.

31. Alves, W.: Intensive Treatment of Schistosomiasis with Antimony (Preliminary Note), South African M. J. 19:171, 1945.

32. Alves, W., and Blair, D. M.: Schistosomiasis: Intensive Treatment with Antimony, Lancet 1:9, 1946.

33. Girgis, B., and Magid, A.: Treatment of Schistosomiasis, Tr. Roy. Soc. Trop. Med. & Hyg. 46:81, 1952.

34. Most, H.; Kane, C. A.; Lavietes, P. H.; Schroeder, E. F.; Behn, H.; Blum, L.; Katzin, B., and Hayman, J. H., Jr.: Schistosomiasis Japonica in American Military Personnel: Clinical Studies on 600 Cases During the First Year After Infection, Am. J. Trop. Med. 30:239, 1950.

35. Khalil, M., and Betache, M. H.: Treatment of Bilharziasis with a New Compound "Fouadin": Report of 2041 Cases, Lancet 1:234, 1930.

36. Khalil, M.: Chemotherapy of Schistosomiasis, J. Egyptian M. A. 18:284, 1935.

37. Rodríguez-Molina, R., and Shwachman, H.: Fuadin Therapy in 150 Cases of Schistosomiasis with a Follow-Up Study of 70 Cases, Am. J. Trop. Med. 27:117, 1947.

38. Hernández-Morales, F.: The Treatment of Schistosomiasis, Puerto Rico J. Pub. Health & Trop. Med. 20:322, 1945.

39. Hernández-Morales, F.; Pratt, C., and Oliver-González, J.: Treatment of Schistosomiasis Mansoni: Evaluation of the Parasitotropic Effects of Fuadin and Tartar Emetic, Puerto Rico J. Pub. Health & Trop. Med. 22:224, 1955.

40. Díaz-Rivera, R. S.; García-Palmieri, M. R.; Ramos-Morales, F., and Marchand, E. J.: La

esquistosomiasis aguda de Manson: II. El tratamiento, Bol. Asoc. méd. Puerto Rico 49:174, 1957.

41. Halawani, A., and Abdallah, A.: Intensive Treatment of Schistosomiasis with Repodral: Preliminary Report of 16 Cases, J. Roy. Egyptian M. A. 29:101, 1946.

42. Harmouda, M.: Intensive Treatment of Bilharzia with Repodral and the Care of the Heart, J. Roy. Egyptian M. A. 29:122, 1946.

43. Mills, G. W.: Treatment of Schistosomiasis, Lancet 1:12, 1946.

44. Azar, J. H.; Pipkin, A. C., and Garabedian, G. A.: An Intensive Treatment of Schistosomiasis with Fuadin, Am. J. Trop. Med. 29:595, 1949.

45. Harris, J. W.: Studies on Drug Induced Hemolytic Anemia, J. Lab. & Clin. Med. 47:760, 1956.

46. Halawani, A.; Shaker, M. H.; Abdallah, A., and Saif, M.: Sulphæmoglobinuria During Administration of Stibophen, Lancet 1:190, 1956.

47. Schick, R.; Ritterband, A., and Lieberman, A. H.: Fuadin Therapy of Schistosomiasis Associated with Ventricular Tachycardia and Death, Ann. Int. Med. 42:392, 1957.

48. Alves, W., and Blair, D. W.: Schistosomiasis: A Review of Work in Rhodesia in 1946, South African M. J. 212:352, 1947.

49. Rivera, J. V.; Rodríguez, H. R., and Pérez-Santiago, E.: Thrombocytopenic Purpura Due to Fuadin (Stibophen), Am. J. Trop. Med. 5:863, 1956.

50. Santiago-Stevenson, D.; Suárez, R. M., and Marchand, E. J.: The Use of BAL in Heavy Metal Poisoning with Particular Reference to Antimonial Intoxication, Puerto Rico J. Pub. Health & Trop. Med. 23:533, 1948.

51. Lippincott, S. W.; Ellerbrook, L. D.; Rhees, M., and Mason, P.: A Study of the Distribution and Fate of Antimony When Used as Tartar Emetic and Fuadin in the Treatment of American Soldiers with Schistosomiasis Japonica, J. Clin. Invest. 26:370, 1947.

52. Schubert, M.: Conditions for Drug Testing in Experimental Schistosomiasis Mansoni in Mice, Am. J. Trop. Med. 28:128, 1948.

53. Schubert, M.: Screening of Drugs in Experimental Schistosomiasis Mansoni in Mice, Am. J. Trop. Med. 28:137, 1948.

54. Schubert, M.: Effect of Drugs During Earliest Stages of Experimental Schistosomiasis Mansoni in Mice, Am. J. Trop. Med. 28:157, 1948.

55. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, Ed. 2, New York, The Macmillan Company, 1956.

56. Newsome, J., and Halawani, A.: The Treatment of Bilharzia in Egypt by Miracil D., Tr. Roy. Soc. Trop. Med. & Hyg. 44:67, 1950.

57. Blair, D. M.; Hawking, F.; Meeser, C. V., and Ross, W. F.: Miracil Clinical Trial on Patients Infected with S. Hematobium and S. Mansoni, Brit. J. Pharmacol. 4:68, 1949.

58. Fisher, A. C.: A Study of the Schistosomiasis of the Stanleyville District of the Belgian Congo, Tr. Roy. Soc. Trop. Med. & Hyg. 28:277, 1934.

59. Vogel, H., and Minning, W.: Über die erworbene Resistenz von Macacus rhesus gegenüber Schistosoma, Ztschr. Tropenmed. u. Parasitol. 4:418, 1953.

Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

A Bibliography of Internal Medicine

Diabetes Mellitus—from Rollo (1798) to Banting (1921)

ARTHUR L. BLOOMFIELD, M.D., San Francisco

Few diseases have stimulated the writing of as many monographs as has diabetes—German, French, and English. From Germany we may note especially those of F. T. von Frerichs (Über den Diabetes, Berlin, August Hirschwald, 1884), of E. Külz (Klinische Erfahrungen über Diabetes mellitus, Jena, Gustav Fischer, 1899), of B. Naumyn (Ref. 16), and G. von Noorden (Ref. 16). The important treatise by E. F. W. Pflüger (Das Glycogen und seine Beziehungen zur Zuckerkrankheit, Bonn, Martin Hager, 1905) must also be mentioned. From France come first and foremost the invaluable treatises of Claude Bernard (Ref. 7, 12) and of Bourchardat (Ref. 3). One may mention also Maréchal's "Recherches sur les accidents diabétiques" (Paris, P. Asselin, 1864), the book by Lecorche (Traité du diabète, Paris, G. Masson, 1877), R. Lepine's imposing treatise (Le diabète sucré, Paris, Felix Alcan, 1909), and Marcel Labbé's smaller but authoritative volume (Le diabète sucré, Paris, Masson et Cie, 1920). England may claim the classical book of Rollo (Ref. 1), whereas from America should be mentioned especially the monograph by Joslin (Ref. 19), which has run through many editions and is still in print (1957). From Scandinavia comes Karl Petren's extensive work (Diabetes-studier, Copenhagen, 1923) and from South America, Pedro Escudera's studies (Tratado de la diabetes, Buenos Aires, Libreria "El Ateneo," 1927).

The best historical summary is to be found in Allen, Stillman, and Fitz' monograph (Ref. 19), where there is also an excellent bibliography. Allen's book (Ref. 19), however, contains the most elaborate list of references to date. Naumyn's treatise (Ref. 16) also has an extensive bibliography.

Accepted for publication Jan. 22, 1958.

Lane Medical Library.

Supported by a grant from the California Foundation for Medical Research.

Diabetes Mellitus

Acetone bodies
References 5, 15
Acidosis
References 10, 13, 15
Antiketogenesis
Reference 20
Cataract
References 4, 6
Clinical
References 1, 3, 16
Coma
Reference 4
Diabetes following extirpation of pancreas
Reference 14
Gangrene
Reference 4

General
References 1, 3, 16
Glycemia
Reference 12
Glycosuria from brain lesions
Reference 7
Islands of Langerhans
References 8, 17
Insulin
Reference 21
Metabolism
Reference 18
Pathology
Reference 17
Relation to pancreas
References 2, 11, 17
Treatment
References 3, 9, 19, 20, 21

1. Rollo, J. Cases of the Diabetes Mellitus with the Results of the Trial of Certain Acids, and Other Substances in the Cure of the Lues Venerea, Ed. 2, London, C. Dilly, 1798.

Rollo's book contains a good summary of knowledge of the disease to date with excellent clinical descriptions. The first case, for example, that of Captain Meredith, is described as follows: "He voids about twelve quarts of urine in twenty-four hours . . . it is of a light straw color, has no smell of urine, but has a whey and violet flavor, and its taste is very sweet. His thirst is excessive . . . there is a clamminess in the mouth and he spits white frothy saliva of a sweetish taste . . . his skin is dry, his face flushed. . . . He is frequently sick and throws up matter of a viscid nature. . . . Mr. Cruikshank took 36 ounces troy weight of urine . . . and it yielded by evaporated three ounces and one dram of saccharine extract, of the appearance of molasses. . . ." (p. 18). Thus sugar was recognized in the urine by tasting it or by obtaining a sticky sweetish substance on evaporation. Rollo and others recognized but failed to interpret the milky character of the serum (lipemia). Current theories blamed diabetes mellitus on disease of the kidneys or stomach. Matthew Baillie thought the kidneys were at fault; Rollo believed that diabetes occurred as a result of a disturbance of the stomach. "The immediate cause . . . is a morbid condition of the stomach, forming or evolving from vegetable substances saccharine matter which is quickly separated as a foreign body by the kidneys" (p. 387). On the basis of this theory Rollo treated his patients with a diet almost exclusively of meat (high protein) and without vegetable matter. With these diets he obtained good results, although some patients found the diet repulsive. "A diet of animal food, with an entire abstinence from vegetable, or other matter capable of forming sugar in the stomach, removes speedily the general symptoms, the saccharine matter, the quantity of urine and its unnatural state" (p. 436). Thus, based entirely on wrong premises Rollo hit on diets not far different from those used 100 years later, which often worked with considerable success. For example, in Captain Meredith's case after a few days, "he drank only three pints of water and made only two quarts of urine, which to him and his servants (who had been in the habit of tasting his urine from curiosity) was not sweet. . . ." (p. 29). The disease was considered a rare one at this time, and Rollo includes many case reports sent to him by prominent physicians, such as Baillie and Abernethy, with their comments. Chapter III, "A Concise Narration of What Has Been Written, or Advanced, Respecting the Diabetes Mellitus," contains the views of Willis, Mead, Metz, Dobson, Cullen, Hone, Darwin, Cawley, and others. In brief, this volume of nearly 500 pages leaves little unsaid about knowledge and views of the disease at the end of the 18th century.

Rollo finally summarizes the subject as follows: "The most remarkable symptoms are, voraciousness and keenness of appetite, or a frequent craving for food, without the feel of entire satiation; . . . intense thirst; a whitish tongue, with red bright sides; red and swelled gums . . . a dry hot skin . . . an increase of clear urine, having a sweetish taste resembling sugar, or rather honey and water; . . . a wasting of flesh;

a weariness and disinclination to motion or exertion with a feeling of weakness; an excoriation, with soreness, of the glans penis, and prepuce. . ." (p. 381). Nothing is said, however, about coma. "No age or constitution seems to be exempted. . . . Mr. Thomas's case affords an example where three brothers had the disease; hence probably there may be some peculiar predisposition. . . . Dissection has shown a change of appearance pretty uniformly in the mesenteric glands and kidneys. . ." (p. 383).

Some of the opinions which Rollo collected from others are of interest. He quotes Dr. Pearson (p. 314), for example, who in discussing a case remarks: "It is plain . . . that I feel inclined to adopt the theory you have so ingeniously framed and so well supported by facts; namely that Diabetes is not essentially a disease of the urinary organs themselves but of the organs of digestion; although you may not think as I do, that the seat is not in the stomach, but in parts less remote from those in which assimilation of nutritious matter takes place. Saccharine matter is not the immediate cause of Diabetes, but the effect of this disease; and if animal food is beneficial and vegetable food is detrimental, it cannot, I think, be shown that it is because the former does not afford sugar and the latter does." He goes on to give reasons as to why kidneys are excretory and not secretory organs and points out that absence of sweet taste in the blood does not rule out the presence of sugar there. Dobson (quoted by Rollo, p. 357) reports a patient in 1772 whose blood contained sugar.* "He supposes that the disease is an affection of the general system, depending on a species of imperfect digestion and assimilation. The saccharine process he imagines is not at an end after the formation of chyle but is still further carried on in the course of the circulation."

2. **Bright, R.** Cases and Observations Connected with Disease of the Pancreas and Duodenum, *M.-Chir. Tr.* 18:1, 1833.

Thomas Cawley (A Singular Case of Diabetes, Consisting Entirely in the Quality of the Urine, with an Inquiry into the Different Theories of that Disease, *London M. J.* 9:286, 1788) is often credited with first noting the association of pancreatic disease and diabetes. The gland in his case did, to be sure, show lesions—calculi and sclerosis—but Cawley failed to correlate them with the disease. Rollo (Ref. 1) and others report numerous autopsies on diabetics without note of pancreatic abnormality. Bright, on the other hand, in a series of cases of obvious pancreatic disease, mostly cancer, noted the association of fatty stools. Patient I of Bright's series began to have marked diabetic symptoms; it was six months later that jaundice appeared, and at autopsy it was found that the head of the pancreas with surrounding glands formed a hard globular mass pressing on the duodenum and bile ducts. Bright, however, missed the significance of the diabetes, which he seems to have regarded as a coincidence. No one at the time of course had any idea of an internal secretion of the pancreas.

3. **Bouchardat, A.** Du diabète sucré ou glycosurie, son traitement hygiénique, Paris, J.-B. Baillière, 1851.

This important monograph represented great advances in the subject. Bouchardat related the disease to lesions of the pancreas, but thought that it was a failure of the external secretion (diastase). He systematized the diet and emphasized the need of restricting carbohydrate until the urine was sugar-free, although he realized that the disease was incurable and "always fatal." He recognized and stressed the importance of exercise in the fresh air in improving the diabetics' power to burn sugar. He tested for sugar in the urine

* An inspection of the original report by Matthew Dobson ("Experiments and Observations on the Urine in a Diabetes, Medical Observations and Inquiries," Ed. 2, London, T. Cadell, 1779, Vol. 5, p. 298) does not convince us that sugar was demonstrated in the blood.

with copper and by polarimetry † and insisted that patients examine their own urine every day, even though sugar-free. He demonstrated sugar in the blood and pointed out that it varied in relation to meals. He failed, curiously enough, to recognize diabetic coma but thought that death was usually due to tuberculosis. He noted the frequency of cataract in glycosurics, and he observed that general failure of vision was worse if albuminuria was present as well as glycosuria. The book was a culmination of Bouchardat's studies on carbohydrate metabolism and diabetes over a period of 15 years.

4. **Marsh, H.** Observations on the Treatment of Diabetes Mellitus, *Dublin Quart. J. M. Sc.* 17:1, 1854.

Emphasis on coma as a termination of diabetes is usually attributed to Marsh. However, all that he says is "I have seen three cases of diabetes terminate in fatal coma." Actually he seems to regard the coma not as the result of the disease but as coincidental. "It so happened that in all these cases opium had long been persisted in, and increased to enormous doses. Many also . . . evinced all the signs and character of tubercular phthisis." One wonders at the apparent rarity of coma as a mode of termination in a case like the following, which is of a sort frequently described in the contemporary accounts: "He was worn down to a perfect skeleton, and died apparently of mere inanition; a mode of death which, though not preceded by acute pain, nevertheless is one of great suffering and distress."

But more interesting is Marsh's observation on vascular occlusion in the legs: "Some years ago I saw a lady about seventy years of age, who had been long affected with diabetes mellitus, carried off suddenly by gangrene of the foot and leg. She complained of coldness in the left limb. A small livid spot on the external side of the great toe caught my eye. On further investigation I found that all pulsation in that limb had ceased. . . . I met in consultation the late Dr. Colles; he told me he had seen two cases of diabetes terminate fatally from obstructed arteries and gangrene."

But other cases of diabetic gangrene were soon reported (see discussion by H. Musset and Francomeau-Dufresne in Review on Diabetes mellitus, *Jahresb. Fortschr. ges. Med.* 4:254, 1860).

5. **Petters, W.** Untersuchungen über die Honigharnruhr, *Vrtljhschr. prakt. Heilk.* 3.81, 1857.

Petters first comments on the aromatic odor of diabetic urine, which has been likened by various observers to sour milk, violets, vinegar, apples, hay, chloroform, horse urine, beer, etc. He also noted a similar odor on the breath of the patient. Petters' curiosity was aroused as to the nature of this aromatic substance, which his colleague, Dr. Lerch, for "various reasons concluded was acetone." A 30-year-old female diabetic gave Petters an opportunity to study the problem. She had a typical very severe case. The urine contained a great deal of sugar; she was very weak, and her breath and urine had the characteristic aromatic odor. "Next morning the patient was found in a state resembling narcosis and her vicinity was pervaded by a chloroform-like odor which was so strong that all the other patients in the ward noticed it. The second assistant even expressed the opinion that the patient had been chloroformed during the night." This syndrome was a new one to those who saw her, although Professor Jaksch had seen two diabetics whose terminal condition was stuporous. "In my opinion the symp-

†G. Lusk ("The Science of Nutrition," Ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 615) says: "Peligot long ago showed that sugar in diabetic urine was glucose." Peligot (Recherches sur la nature et les propriétés cliniques des sucres, *Compt. rend. Acad. sc.* 7:106, 1838), to be sure, says that "sugar of diabetes and sugar of honey have exactly the same composition and properties, and constitute a single substance which we propose to call *glucose*." But he assigns to it a formula $C_{36}H_{36}O_{24}+4H_2O$.

toms were due to poisoning by the unknown substance." Thirty hours later the patient died. In the autopsy report the pancreas is not mentioned. In the stomach contents chemical examination showed "that the questionable substance could be none other than Acetone=$C_6H_6O_2$." Petters also demonstrated acetone in the blood, and he concludes that the "narcosis of our patient and her subsequent death were consequent to poisoning of the blood by Acetone." Petters failed however to discover the source of the acetone, although he concluded that it could not have been formed directly from sugar. He was inclined to think it was derived from abnormal fermentation in the stomach.

6. **France:** On cataract in Association with Diabetes Mellitus, *Ophth. Hosp. Rep.* 1:273, 1859.

We have already pointed out that Bouchardat noted the frequent association of cataract with glycosuria. France, however, wrote systematically on the subject. "The subjoined cases may, perhaps, be of service in directing the notice of the profession to a complication, and apparently a cause of cataract, which has been but cursorily alluded to by authors." He then reports the cases of four diabetics aged ?, 48, 19, and 30 years, respectively, who all developed cataracts: "but the aqueous chambers were rendered shallow in consequence of the irides being pressed towards the cornea by large, soft, lenticular cataracts. . . . There can apparently exist no doubt as to the dependence of the cataracts upon the diabetic malady." He notes after operation the "indisposition of the cornea to heal." In Germany at the same time von Graefe agreed on the diabetic etiology of some forms of cataract (see discussion of diabetes mellitus in *Jahresb. Fortschr. ges. Med.* 4:257, 1860).

7. **Levrat-Perroton, F.** Quelques considérations sur un cas de glycosurie déterminée par une tumeur colloide renfermée dans le 4ième ventricule, Thèse, Paris, 1859. (Abstract in *Jahresb. Fortschr. ges. Med.* 4:254, 1860.)

Claude Bernard (Leçons sur la physiologie et al pathologie du système nerveux, Paris, J.-B. Baillière et Fils, 1858, Vol. 1, p. 397) brought together in 1858 his classical work on production of glycosuria by puncture of the floor of the fourth ventricle. It remained for clinical lesions in this region to be shown to cause the same result. Levrat-Perroton reported a woman in whom the symptoms of brain tumor and diabetes developed simultaneously and in whom autopsy showed a tumor pressing on the fourth ventricle, "a tumor the size of a walnut which completely filled the distended IV ventricle." The tumor seemed to arise from the choroid plexus. F. von Recklinghausen (Ref. 11) described the case of a man who after a blow on the head developed severe diabetes. At autopsy six months later a tumor was found in the fourth ventricle which was narrow and occupied toward the rear by the tumor $\frac{5}{8}$ by $\frac{3}{8}$ in. thick. This tumor was also thought to originate in the choroid plexus. Neither of these writers refers to the work of Claude Bernard, although E. Fritz (Du diabète dans ses rapports avec les maladies cérébrales, *Gaz. hebd.* 4:264, 294, 344, and 374, 1859) gives an elaborate review of previous reports on the association of diabetes with all sorts of cerebral lesions, with numerous case reports and with discussion of clinical and experimental relations.

8. **Langerhans, P.** Zur mikroskopischen Anatomie der Bauchspeicheldrüse, Inaugural-Dissertation, Berlin, 1869.

Whoever thinks that Langerhans gave a clear modern description of the islands will be disappointed. Langerhans was an inexperienced microscopist, as he himself modestly states. "I only beg pardon if these lines fall into the hands of an experienced microscopist and he find in them too much

that is well known and too little of the unknown." Langerhans, in 1869, also worked with relatively inadequate methods. He traced out, however, the relation of acinar cells to ducts and then found other cells which he describes. "These cells are small, irregular polygonal structures; their content is completely homogeneous, bright and free of any granules, their nucleus light, round and of medium size. Their diameter is 0.0096 to 0.012 millimeters, that of the nucleus 0.0075 to 0.008. These cells lie for the most part near one another but peculiarly distributed in the parenchyma of the gland . . . by low magnification one sees regularly scattered through the gland roundish intensely yellow colored dots . . . higher magnification shows that the dots consist exclusively of 'our' cells. These are then heaped up into roundish clusters scattered through the parenchyma. The clusters show for the most part a diameter of 0.1 to 0.24 millimeters."

It would take us too far afield in this bibliography to give details of further studies of the islands. The early work is thoroughly reviewed by Opie (Ref. 17, p. 59). More recent papers are those of R. R. Bensley (Studies on the Pancreas of the Guinea Pig, *Am. J. Anat.* 12:297, 1911) and E. Clark (The Number of Islands of Langerhans in the Human Pancreas, *Anat. Anz.* 43:81, 1913).

9. **Harnack, E.** Zur Pathogenese und Therapie des Diabetes mellitus, *Deutsches Arch. klin. Med.* 13:593, 1874.

Harnack stressed the fact that sugar in the urine of diabetics was related to the carbohydrate intake. "First we seem to have brought proof that the quantity of sugar in the urine of a diabetic bears a direct proportion to the quantity of ingested carbohydrate, a circumstance which supports the view that diabetes essentially depends on impaired metabolism of the carbohydrate which is taken in." He noted that excretion of sugar was not increased by ingestion of glycerine and advised its use in therapy, a procedure still in vogue 40 years later.

10. **Kussmaul, A.** Zur Lehre vom Diabetes mellitus, *Deutsches Arch. klin. Med.* 14:1, 1874.

Kussmaul, a keen clinical observer, was struck by the association of coma and a peculiar form of dyspnea in three diabetics which made him believe that he was dealing not with mere coincidence but with a fundamental organic disturbance. The cases are reported in vivid detail. "The breathing was loud, accelerated [36] and the respiratory excursions strikingly great. Gigantic costo-abdominal inspirations alternated with gigantic expirations." All the accessory respiratory muscles were used, but there was no cyanosis nor the slightest evidence of obstruction. He contrasted the general exhaustion and prostration with the violence of the respiratory movements and he used the term "air hunger." "We are therefore forced to the question whether the cause of this dyspnea is not to be sought in a chemical contamination of the blood by a substance which exerts a tremendous stimulus of the respiratory centers while access of oxygen to them is unmodified." Kussmaul discusses the possibility of CO_2 retention but dismisses it. "It seems probable that it is a little due to a tremendous accumulation of CO_2 as to oxygen lack. . . . It must come from an intoxication of some other sort." Kussmaul raises the question of whether acetonemia is responsible, but he thinks the evidence is against this view.

Kussmaul also clearly recognized dehydration in diabetic acidosis. In an attempt at transfusion in a coma patient a vein was opened, and even with the tourniquet there came out only "a thick, brown-red blood, drop by drop which clotted immediately." He also noted great abdominal pain in precomatose patients.

11. **Lancereaux, E.** Notes et réflexions à propos de 2 cas de diabète sucré avec altération du pancréas, *Bull. acad. méd.*, Paris 6:1215, 1877.

Lancereaux is usually mentioned as the first definitely to claim a causal relation of pancreatic disease to diabetes. "Taking into

account the special characters of diabetes in the cases of disease of the pancreas, and taking into account the phenomena produced in animals by the destruction of this same organ, we believe we can conclude that there exists a causal relation between serious lesions of the pancreas and diabetes mellitus." This view was based on two fatal cases with extensive destruction of the pancreas; in one there was an obscure almost total atrophy, and in the other, destruction of practically the whole organ by calculi in the duct of Wirsung. "The pancreas was so to speak totally destroyed." Lancereaux also collected some scattered cases from the literature from Cawley on (Ref. 2) in which gross disease of the pancreas was associated with diabetes. F. von Recklinghausen (Auserlesene pathologisch-anatomische Beobachtungen, *Arch. path. Anat.* 30:360, 1864), for example, reports two cases of diabetes in which at autopsy gross atrophic lesions of the pancreas were found. "Lesions . . . which doubtless are directly related to the diabetes." But still no one was aware of an internal secretion.

12. **Bernard, C.** Leçons sur le diabète et la glycogénèse animale, Paris, J.-B. Baillière et fils, 1877.

Claude Bernard, in these classical lectures on diabetes, clearly states the principles of glycemia and glycosuria. "Thus the sugar which is excreted by the kidney is not produced by that organ. It exists preformed in the blood . . . glycosuria is simply the consequence of glycemia" (p. 125). Bernard repeats his method of measuring blood sugar which he first described years before (Leçons de physiologie expérimentale appliquée à la médicine, Paris, J.-B. Baillière et fils, 1855, p. 45). Bernard stresses the invariable presence of sugar in the blood of healthy people as well as of diabetics, although the test must be made promptly or the sugar disappears. This view has not been generally accepted but is correct. "There is only one kind of glycemia; it is constant, permanent, whether during diabetes or outside of this diseased state. To be sure it has various degrees: Glycemia below 3 to 4 per 1000 does not lead to glycosuria; but above this glycosuria is produced. Also after a meal glycemia increases, fasting, it diminishes in degree. . . . One sees then that the problem is complex but it never ceases to be a *physiological* problem. The transition from the normal to the pathological can not be defined and nothing shows the intimate relation between physiology and pathology better than diabetes" (p. 132). Lectures 5 and 6 are devoted to an interesting and definitive historical survey of glycemia. He discusses the origin of the blood sugar: "The liver normally produces the sugar which is spilled into the circulation" (p. 291). The entire book is rich in fundamental observations.

13. **Stadelmann, E.** Über die Ursachen der pathologischen Ammoniakauscheidung beim Diabetes mellitus und des Coma diabeticum, *Arch. exper. Path. u. Pharmakol.* 17:419, 1883.

E. Hallervorden (Über Ausscheidung vom Ammoniak im Urine bei pathologischen Zuständen, *Arch. exper. Path. u. Pharmakol.* 12:237, 1880) studied ammonia excretion systematically in various diseases. He noted especially large outputs in cases of diabetes mellitus. He sought the cause of the ammonia excretion in a high output of acid, but determinations of phosphate and sulfate showed no relation to the amount of ammonia. He also gave a diabetic large amounts of bicarbonate of soda, but not the slightest decrease in ammonia, which he expected, was found. Stadelmann continued these studies in diabetics and confirmed the great increase in ammonia excretion in some cases. He raised the question of whether the ammonia did not serve to neutralize acid and thus to defend the fixed base of the body. Tests for acetone, curiously enough, showed little or none. He concluded, however, that the unknown acid in the urine was a fixed organic substance, probably "Krotonsaure." He suggested the

injection of sodium bicarbonate as treatment for diabetic coma.

O. Minkowski (Über das Vorkommen von Oxybuttersäure im Harn bei Diabetes mellitus, *Arch. exper. Path. u. Pharmakol.* 18:35, 1884) soon showed that the acid substance in urine was β-oxybutyric acid (a substance closely related to Crotonsäure), and he raised the question, as did Stadelmann, of whether diabetic coma was not due to acid intoxication with this substance. Intravenous injection of bicarbonate improved a patient's condition markedly, although only temporarily, the urine remaining acid, and these facts Minkowski felt supported the theory of acid intoxication. On the basis of these ideas Stadelmann (Weitere Beiträge zur Behandlung des Diabetes mellitus und des Coma diabeticum, *Deutsches Arch. klin. Med.* 37: 580, 1885) recommended an alkaline potion of citric acid, sodium bicarbonate, glycerin, and water in the treatment of diabetic coma. Finally Stadelmann (Über die Behandlung gewisser Formen von Diabetes mellitus mit Alkalien, *Deutsches Arch. klin. Med.* 38: 302, 1886) pointed out that huge doses of bicarbonate were necessary to render the urine in diabetic coma alkaline, and he thought this treatment would be of value in diabetes. It is of interest that none of these workers mention the observations of Petters (Ref. 5).

14. von Mering, J., and Minkowski, O. Diabetes mellitus nach Pancreas Extirpation. *Arch. exper. Path. u. Pharmakol.* 26:371, 1890.

The writers remind us that the effects of removal of the pancreas have been observed for 200 years with dubious and inconstant results because of technical difficulties which prevented really total extirpation. After devising a successful method, they showed that "after complete removal of this organ the dogs become diabetic. It is not a question of a transitory glycosuria; the dogs develope genuine permanent diabetes mellitus which corresponds in every respect with the severest forms encountered in man." The diabetes began promptly after pancreas extirpation. The dogs became enormously hungry and thirsty; they developed polyuria and showed rapid loss of weight and strength. In addition to sugar, acetone bodies often appeared in the urine. The blood sugar was elevated. The glycogen content of organs rapidly was reduced to traces. Mering and Minkowski laid special stress on partial extirpation, after which diabetes failed to appear. They made the important observation that ligation of the pancreatic ducts led to atrophy of the organ but *not* to diabetes even though the animals developed fatty diarrhea. "We can conclude that the cause of the diabetes after pancreas extirpation in no way depends on the absence of pancreatic juice in the intestine because diabetes occurs even if the animal is fasted and the bowel is empty. So there can be no question of absence of effect of pancreatic juice on the ingesta, but rather a disturbance of the internal intermediary metabolism of the organism." What is the nature of this disturbance? It seems that it must be either an accumulation of some abnormal product or the elimination of some normal function of the pancreas. They ruled out the first possibility by transfusion of blood from diabetic dogs to normals without any deleterious effect and came to the epoch-making conclusion that "diabetes can only be the result, in dogs with pancreas extirpation, of the cessation of a function of this organ which is absolutely essential for the utilization of sugar in the organism; we have to deal here with a special hitherto unrecognized function of the pancreas." They first suspected a constant dextrose-nitrogen (D:N) ratio in total diabetes.

Minkowski (Untersuchungen über den Diabetes mellitus nach Extirpation des Pancreas, *Arch. exper. Path. u. Pharmakol.* 31:85, 1892) later, in a tremendous article of over 100 pages, reviewed further work of his own and of others. A few of the high spots of the monograph are the demonstration of a nearly fixed D:N ratio in

totally diabetic dogs, of mild and moderately severe diabetes in dogs after partial extirpation of the pancreas, and of the fact that diabetes was lessened by subcutaneous implants of pancreas and worsened when the transplants were excised. He showed that phlorizin diabetes had nothing to do with diabetes mellitus and that levulose even in diabetic animals led to glycogen deposition in the liver. He still thought, however, that the acetone bodies were derived from protein.

Mering and Minkowski's observations were followed by a flood of work which is summarized by D. Hansemann (Die Beziehungen des Pancreas zur Diabetes, *Ztschr. klin. Med.* 26:191, 1894). This writer was puzzled by the fact that diabetes could occur without histological lesions of the pancreas. He failed to recognize the islands as such, however, and felt that if lesions were present in diabetics they were usually a general atrophy. The histology of the pancreas in diabetes has puzzled many later writers as well (Ref. 8) even after Opie (Ref. 17) had assigned a causal role to the islands.

15. Geelmuyden, H. Über Aceton als Stoffwechselproduct, *Ztschr. physiol. Chem.* 23:431, 1897.

Geelmuyden points out that the current point of view indicated that acetone bodies came from protein but that doubt was cast on this position by W. Weintraud (Über die Ausscheidung von Aceton, Diaceticsäure und B-Oxybuttersaüre beim Diabetes mellitus, *Arch. exper. Path. u. Pharmakol.* 34:169, 1894), who showed that acetonuria could exist even when the patient was in N equilibrium. He also called attention to an old observation that acetonuria was reduced by ingestion of carbohydrate. G. Rosenfeld (Die Grundgesetze der Acetonurie und ihre Behandlung, *Zentralbl. inn Med.* 16:1233, 1895) confirmed this fact, as did F. Hirschfeld (Beobachtungen über die Acetonurie und das Coma diabeticum, *Ztschr. klin. Med.* 28:176, 1895). Although both of these workers report elaborate metabolic observations, neither got the idea that acetone bodies might be derived from fat.

Geelmuyden was the first to propose this concept. As a result of metabolic observations on animals and man he concludes: "Metabolism of fat in the body seems to be the essential cause of acetonuria, and inasmuch as highgrade acetonuria occurs in starvation, metabolism of body fat and fat given in the diet seem to behave equally." A. Magnus-Levy (Untersuchungen über die Acidosis im Diabetes mellitus und die Saüreintoxication im Coma diabeticum, *Arch. exper. Path. u. Pharmakol.* 45:389, 1901) carried the subject further and raised the question of whether the acetone bodies might be derived not from preformed volatile fatty acids but from break-down of long-chained higher fatty acids. Magnus-Levy (Die Acetonkörper, *Ergebn. inn. Med.* 1:352, 1908) later reviewed in authoritative fashion the whole subject of the acetone bodies: derivation, antiketogenic substances, occurrence in diabetes. He regarded it as settled that the main source of acetone bodies was fatty acids; he supported the view of derivation from higher fatty acids by β-oxidation. Later a great deal of work was done in this country on the subject, and P. A. Shaffer (Antiketogenesis: Its Mechanism and Significance, *Medicine* 2: 375, 1923) summarized the whole problem. He pointed out that ketone bodies, while derived mainly from fatty acids, also arose in the metabolism from certain amino acids. He supported the old and prevailing view that to prevent the accumulation of acetone bodies there must be a certain amount of glucose in the metabolic mixture. As G. Rosenfeld had put it, "Fats burn only in the fire of carbohydrates." Shaffer laid stress on the quantitative relationships. W. C. Stadie (Fat Metabolism in Diabetes Mellitus, *J. Clin. Invest.* 19:843, 1940) questioned the theory that fatty acids were broken down by β-oxidation as well as the view that combustion of fatty acids was dependent on glucose in the metabolic mixture. He showed that "the diabetic animal

utilizes ketone bodies in the periphery abundantly and independently of carbohydrate oxidation," and he concluded that if too little carbohydrate is being burned the body must obtain its calories from fat. But since there is a limit to the amount of fatty acid which can be burned daily, the excess then appears as ketone bodies. Stadie (Fat Metabolism in Diabetes Mellitus, *Ann. Int. Med.* 15:783, 1941) later stated his views precisely: "The diabetic who . . . is unable to utilize carbohydrate . . . must fall back on fat for his energy requirements. Part of this need is met by the initiation and complete fat oxidation in the muscles themselves. However a considerable fraction . . . of the total caloric needs from fat is obtained by a preliminary oxidation of fats in the liver to ketone bodies only . . . . These hepatic ketone bodies are freely utilized for energy by the periphery without insulin and without the necessity of simultaneous carbohydrate oxidation . . . when the demand for fat calories exceeds a certain level, approximately 2.5 gm. of fat/kg./day for the resting state, ketone bodies in excess of needs are formed by the liver. The excess is excreted as ketones in the urine. If this excessive fat catabolism continues unchecked, ketosis and coma follow."

16. Naunyn, B. Der Diabetes Mellitus. Vienna, Alfred Hölder, 1898.

This monumental work by the great Strassburg clinician was the classical storehouse of knowledge of diabetes for many years (Ed. 2, 1906). Naunyn was the standard authority on treatment until the Allen era, and indeed Joslin refers to practice in his time as the Naunyn era. In close competition was Carl von Noorden, whose book "Die Zuckerkrankheit und ihre Behandlung" (Berlin, August Hirschwald, 1895) ran through many editions, the eighth appearing in collaboration with S. Isaac as late as 1927 (Berlin, Julius Springer Verlag), well into the insulin era. In this country the paper of T. C. Janeway (The Dietetic Treatment of Diabetes, *Am. J. M. Sc.* 137:313, 1909) represented the best American practice before the Allen era.

17. Opie, E. L. On the Relation of Chronic Interstitial Pancreatitis to the Islands of Langerhans and to Diabetes Mellitus, *J. Exper. Med.* 5:397, 1901.

M. E. Laguesse (Sur la Formation des îlots de Langerhans dans le pancreas, *Compt. rend. Soc. biol.* 5:819, 1893) on histological grounds was the first to suggest that the island of Langerhans represented an organ of internal secretion.‡ Two years later Edward A. Schäfer (Address in Physiology on Internal Secretions, *Lancet* 2:321, 1895) clearly enunciated the doctrine of an internal secretion by the cells of the islands of Langerhans which was essential for carbohydrate metabolism. He does not state, however, that their internal secretion influences carbohydrate metabolism, as quoted by Opie. L. W. Ssobolew (Über die Structur der Bauchspeicheldrüse unter gewissen pathologischen Bedingungen, *Zentralbl. allg. Path.* 11:202, 1900) concluded on historical grounds also that the islands had an internal secretory function related to the "sugar economy of the body." He ligated the pancreatic ducts and produced atrophy of the acinar tissue with preservation of the islands. No diabetes appeared in these animals, which fortified his views, as did the failure to find islands at autopsy in two diabetics. Opie, meanwhile, had been working on the subject and described various forms of pancreatitis in relation to diabetes. His main piece of evidence, however, was the case of a diabetic girl in whom at autopsy the islands were converted into hyaline masses. He concludes, "A relationship has been observed between lesions of the islands of Langerhans and the occurrence of diabetes mellitus." Later *Zen-*

‡R. Lepine (Nouvelle théorie du diabète, *Lyon méd.* 62:619, 1889) suggested that diabetes mellitus might be due to lack of a ferment secreted into the blood stream by the pancreas, but he thought it was produced by the pancreatic tissues in general and made no allusion to the islands of Langerhans or to any cells which play a specific role.

tralbl. allg. Path. 11:527, 1900) he reports and pictures the pancreas from another fatal case of diabetes in which the islands showed remarkable hyaline changes, and he concludes firmly, "Since diabetes is absent when, as a result of duct obstruction, the secretory portion of the gland undergoes great alteration, though the islands are spared, the conclusion is justified that it is these structures which influence carbohydrate metabolism." Opie's work is summarized in his book on "Disease of the Pancreas: Its Cause and Nature," Philadelphia, J. B. Lippincott Company, 1903, Chap. 5, 10, and 11.

A great flood of work on the subject now poured forth, and many observers were puzzled by being unable to find overt lesions of the islands or indeed of the pancreas as a whole in diabetes. I can only select a few papers on this subject. R. L. Cecil (A Study of the Pathological Anatomy of the Pancreas in 90 Cases of Diabetes Mellitus, *J. Exper. Med.* 11:266, 1909) made very careful pathological observations. He concluded that anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus and that in diabetes associated with lesions of the pancreas the islands constantly show changes (sclerosis, hyaline degeneration, infiltration with leukocytes, and hypertrophy). In some cases the lesion was limited to the islands. In 12% of the cases the pancreas exhibited no disease, and in general lesions were more frequent as age advanced. Cecil, as well as K. A. Heiberg (Die Entstehungsweise der Inselveränderungen und ihr Verhalten bei Diabetes mellitus, *Beitr. path. Anat.* 51:1911), noted in certain diabetics a diminution in the number of islands. But R. H. Major, working in Ophüls' laboratory (The Pathological Anatomy of the Pancreas in Diabetes, *J. M. Res.* 31:313, 1914), was skeptical. He found that 54% of the cases showed normal islands of Langerhans and that whereas fibrosis of the islands was present in 46% it was no more marked than in nondiabetic cases. He concluded that "in many cases of diabetes mellitus, therefore, we have no anatomical evidence to prove that the diabetes is due to pancreatic disease," and this raised the question of purely functional distempers of the islands. F. M. Allen in his book (Studies Concerning Glycosuria and Diabetes, Boston, W. Leonard, 1913, p. 911) gives a comprehensive review of various opinions on the relation of the islands to diabetes. But W. F. Gibb Jr., and V. W. Logan (Diabetes Mellitus: A Study of 147 Autopsies, *Arch. Int. Med.* 43:376, 1929), after a very thorough study of the lesions, were still perplexed and conclude "It is hoped that a simple test may be devised to enable one to correlate the severity of the diabetic condition. Until this has been done, it seems impossible to relate the clinical and pathological observations in diabetes mellitus." The whole subject is authoritatively reviewed and documented in the book by Shields Warren and Philip M. LeCompte (The Pathology of Diabetes Mellitus, Ed. 3, Philadelphia, Lea & Febiger, 1952, p. 31).

18. **Benedict, F. G., and Joslin, E. P.** Metabolism in Diabetes Mellitus, Washington, D. C., Carnegie Institution, Publication No. 136, 1910.

This is a lengthy report of observations on the metabolism of diabetes measured with the help of a respiration chamber. These classical experiments showed no *qualitative* differences in the metabolism in diabetes as against normals with allowance for the type of food burnt. Such matters as the respiratory quotient, the influence on the respiratory exchanges and the total catabolism, and the influence of muscular work upon metabolism in diabetes are discussed. In another monograph (A Study of Metabolism in Severe Diabetes, Washington, D. C., Carnegie Institution, Publication No. 176, 1912) these observations were amplified.

19. **Allen, F. M.** Studies Concerning Glycosuria and Diabetes, Boston, W. M. Leonard, 1913.

Buried in a vast amount of extraneous material one finds the experiments which

radically altered the treatment of diabetes and initiated the "Allen era" of undernutrition. The essential observations showed that partially depancreatized diabetic dogs died if fed liberally but survived if undernourished. The treatment was promptly applied to patients. By 1916 E. P. Joslin (The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1916) had taken up the "starvation," method and indeed this was the only plan of treatment advised. "The introduction of fasting and the emphasis on physical exercise in the treatment of diabetes by Dr. F. M. Allen . . . has decidedly changed the outlook for this class of patients. 'Fasting' is itself a distinct advance but the practical simplification of treatment which it entails is an almost greater advantage. Now doctor and patient may know at once whether the treatment is successful" (preface, p. V). Allen himself (F. M. Allen, E. Stillman, and R. Fitz: Total Dietary Regulation in the Treatment of Diabetes, New York, The Rockefeller Institute for Medical Research, Monograph No. 11, 1919) reported in exact detail the treatment of many patients by his method.

20. **Woodyatt, R. T.** Objects and Method of Diet Adjustment in Diabetes, *Arch. Int. Med.* 28:125, 1921.

While the Allen method had in some ways been an advance over other schemes of therapy, it was not altogether satisfactory. In order to attempt control in severe cases the patient had to be reduced to a skeleton. Woodyatt's classical paper dealt a serious blow to the Allen treatment. Woodyatt pointed out that the important thing was not what one fed in terms of protein, carbohydrate, and fat but what the patient burned, i. e., the composition of the metabolic mixture. He first emphasized to clinicians that while ingested glucose yielded in the body only glucose, 100 gm. of protein yields 58 gm. of glucose and about 46 gm. of fatty acid (F. A.), and 100 gm. of fat yields 10 gm. of glucose and 90 gm. of fatty acid. He pointed out further that if the ratio F. A.:G in the metabolic mixture was greater than 1.5:1, then acetonuria was likely to develop. Woodyatt drew practical applications: "For mental calculation, if one knows that a patient can actually utilize a certain number of grams of glucose, take this number times seventeen as the approximate number of calories that he will be capable of using at best without glycosuria if the diet is most favorably balanced. Then, knowing the patient's weight the severity or the mildness of the situation becomes apparent." Thus Woodyatt for the first time put the diabetic diet on a really rational basis. No student of the disease can afford not to study this paper carefully. W. S. McCann, R. R. Hannon, W. A. Perlzweig, and E. H. Tompkins (Studies of Diabetes Mellitus: II. Results of Treatment by Diet Adjustment with Reference to Maintenance Requirement and the Ketogenic-Antiketogenic Balances, *Arch. Int. Med.* 32:226, 1923) made important studies of the application of Woodyatt's principles by giving enough calories to cover the maintenance requirement for rest in bed, reducing the level of protein metabolism by means of a low-protein intake, and maintaining proper antiketogenic balance in the metabolic mixture. Their charts show beautifully how even severe diabetics may become sugar- and acetone-free with fairly adequate caloric intake. So the matter stood when insulin became available, although even with insulin the principles of diet brought out by Woodyatt and by McCann still hold good.

21. **Banting, F. G., and Best, C. H.** The Internal Secretion of the Pancreas, *J. Lab. & Clin. Med.* 7:251, 1921.

S. Zuelzer (Über Versuche einer specifischen Fermenttherapie des Diabetes, *Ztschr. exper. Path. u. Therap.* 5:307, 1908) made some rudimentary attempts to control diabetes with intravenous injections of "extracts of pancreas," but these experiments were obviously inadequate. Later J. R. Munlin and B. Kramer (The Influence of Pancreatic and Duodenal Extracts on the Glycosuria and the Respiratory Metabolism of Depancreatized Dogs, *J. Biol. Chem.*

15:365, 1913), using intravenous infusions of pancreatic extract made from cow pancreas, concluded that this procedure "is not yet a measure of any practical importance in restoring to the depancreatized dog the ability to burn sugar." McLeod reviews in detail all of the early failures.

Thus no one had been able to produce an extract of pancreas which was really effective until Banting's attempt. Banting followed the old observation (Refs. 14, 17) that ligation of the pancreatic ducts was followed by atrophy of the acinar tissue with preservation of the islands. Ten weeks or so after ligation the remaining pancreas was excised and watery extracts of it were injected intravenously into depancreatized diabetic dogs. Banting and Best's charts show indubitable lowering of blood sugar. Their conclusions were as follows:

"Intravenous injection of extract from dog's pancreas, removed from seven to ten weeks after ligation of the ducts, invariably exercises a reducing influence upon the percentage of sugar in the blood and the amount of sugar excreted in the urine . . . . The extent and duration of the reduction varies directly with the amount of extract injected. Pancreatic juice destroys the active principle of the extract . . . . Boiled extract has no effect on the reduction of blood sugar."

Thus, after many years a specific agent for the control of diabetes mellitus was discovered. The vast amount of work on definitive methods of extraction, standardization, commercial preparation, and clinical trials was to come later, but as early as 1924, W. R. Campbell and J. J. R. McLeod (Insulin, *Medicine* 3:195, 1924), in whose laboratory Banting and Best's work was done, wrote a lengthy review of the subject with over 300 references. Banting himself wrote the story of "The History of Insulin" (*Edinburgh M. J.* 36:1, 1929) in a fascinating and autobiographical fashion at the time when honors were coming thick and fast. Banting's premature death in the service of his country in World War II stimulated Lloyd Stevenson to write a eulogistic biography (Sir Frederick Banting, Toronto, Ryerson Press, 1946).

Books

EDITED BY WILLIAM B. BEAN, M.D.*

Conference on Atherosclerosis and Coronary Heart Disease. Price, not given. Pp. 133. New York Heart Association, Inc., 270 Park Ave., New York 17, 1957.

The New York Heart Association has published several notable symposia and in other respects exerted a strong influence for the advance of cardiology not only in New York but throughout this country and the world. The papers reported at this one-day meeting stress particularly clinical aspects of diagnosis and treatment, with emphasis on current aspects of pathogenesis. The last half of the symposium deals with epidemiological aspects, rehabilitation, and cardiology as it related to the community and to public health. This excellent series of discussions will be useful to cardiologists, public health workers, and those doing general practice and internal medicine.

WILLIAM B. BEAN, M.D.

Medical Ethics: A Guide to Students and Practitioners. By Maurice Davidson, D.M., F.R.C.P. Price, 20 shillings net. Pp. 165. Lloyd-Luke (Medical Books), Ltd., 49 Newman St., London, W. 1, 1957.

Many distinguished British physicians have contributed to this book by Maurice Davidson. It constitutes a formal presentation of problems of medical ethics, medical mores, and medical manners designed to guide students and practitioners but relating also to teachers and investigators. The symposium as presented took its form largely on the basis of a letter to the editor from an undergraduate medical student. Of great interest to physicians in this country will be the essay on the structure and functions of the General Medical Council in England, which is just 100 years old this year. It serves the function of an official medical judicial and executive council, monitoring the actions of physicians, helping them formulate rules and regulations for appropriate behavior, and providing a tribunal before which anyone charged with major dereliction may appear with or without counsel. The fact that nothing like this exists in the United States suggests that we have a serious flaw in medicine's own internal control of physicians, whether as housekeeping or policing. The problems discussed include the doctor's relationship to patients, colleagues, religion, the law, and his own family; a consideration of the moral and legal aspects of contraception, therapeutic abortion, sterilization, and artificial insemination; a perceptive essay on what to tell the gravely ill patient or one who has to undergo a serious operation; the management of the hopeless case, and the care of the dying, as well as an essay on human experimentation and experimental medicine, with a discussion of the Hippocratic Oath completing the book. Our heritage from Britain in government, the law, language, and customs is pervasive. The debt of American medicine to Britain becomes clear in these pages, where wise and learned men, leaders of British medicine and British medical thought, have addressed themselves to matters of outstanding importance. The only discordant note is the instructions for performing euthanasia, which, though written by Hoyle, is not according to Hoyle.

WILLIAM B. BEAN, M.D.

John Jacob Abel, M.D. Compiled and distributed by the Williams & Wilkins Company. Price, not given. Pp. 80, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

A point usually overlooked in historical discussions of the founding of The Johns Hopkins Hospital and Medical School is the considerable contribution of men trained at Michigan to Johns Hopkins. In the first group one mentions Mall, Abel, Howell, and Hurd. This little book about Dr. Abel was published as a gesture of thanks and tribute by the Williams & Wilkins Company in recognition of Abel's contribution to medical journalism and their particular interest in medical journalism. It is a timely recognition of a man who had a large influence in the formation and development of pharmacology in this country. There are several tributes and sketches. In addition several of the articles upon which the enduring fame of Dr. Abel lasts are reprinted. His notable contributions to the isolation of epinephrine, the crystallization of insulin, and the original suggestion for an artificial kidney are reprinted in

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

full. This little volume is an excellent reminder of the contributions of one man who had an important part in the growth and coming of age of pharmacology. Its preparation and production by the Williams & Wilkins Company is an interesting example of a biographical contribution which will please Abel's admirers and be of interest to students of history and medicine.

WILLIAM B. BEAN, M.D.

Practical Allergy. By M. Coleman Harris, M.D. and Norman M. Shure, M.D., M.S. Price, $7.50. Pp. 471, with 25 illustrations. F. A. Davis Company, 1914-1916 Cherry St., Philadelphia 3, 1957.

The authors have prefaced this book with the comments that the book is oversimplified and is for the doctor who does not devote much time to allergy. Within the book the total field of allergy is covered by giving relatively brief surveys or explanations on every phase of allergy. Even the proper preparation of equipment is described. While the book contains much definitive information, its value diminishes, insofar as giving decisive guidance to novices, by the use of too many qualifying words or statements. There is no date of publication in the book.

JAMES H. JOHNSON, M.D.

The Student-Physician: Introductory Studies in the Sociology of Medical Education. Edited by Robert K. Merton, George G. Reader, M.D., and Patricia L. Kendall. Price, $5. Pp. 360, with illustrations. Published for the Commonwealth Fund by Harvard University Press, Cambridge 38, Mass., 1957.

Anyone interested in teaching medical students should read "The Student-Physician." He will have to be very much interested in it to read the whole thing, because at least parts of it are written as though the writer were paid a bonus for superfluous words. Here is an example: "But whatever the consequences of these differences and these remain to be identified, it can be seen that the criteria and procedures for admission not only have the manifest function of selecting individuals more or less suited to the role of physician but also the indirect and latent function of producing a distinctive social environment for each student. In other words, the procedures and criteria of selection not only involve the psychological consideration of the personal qualities of each individual student but also the sociological consideration of the composition of the total student body." Far too many of the words are padding and serve no useful purpose. The ideas might be condensed as follows: But whatever the results of these differences, procedures, and criteria for admission, they do select persons suited to the role of physician. They also help produce a social environment for each student. Selection involves psychological considerations of the personal qualities of individual students and sociological aspects of the whole student body. This has only about half the words and is at least as clear.

A few words or combinations from the jargon of the sociologists disturb the reader, but as one moves along in the book and becomes accustomed to the special lingo useful ideas actually emerge. The background of the experiments and the theoretical constructs on which they were based are discussed in detail. There are several interesting studies of reasons for decisions to study medicine and other professions, though I sometimes wonder if sociologists do not tend to get just a little bit bewildered by their enthusiasm for their own curious expressions, talking about "structural facts," "proper operating decisions," "to comment insightfully." To me the second half of the book was more valuable than the first, dealing with the necessity for training for uncertainty, the preference of students for particular types of patients and problems, and the development of the professional self-image. Then there is an analysis of the observations and the methods of recording, together with complete appendices. Much of this is subjective, and this work lacks the scientific critique necessary in an experiment in pedagogy. The book deals with what was observed in the changed curriculum. Without firm agreement of what "the good physician" should be, we have no benchmark against which to compare the products of any system of medical education. Nevertheless, anyone genuinely interested in medical education will find much of interest in this study. It should be required reading for all teachers in medical schools. Despite the somewhat turgid prose and the jargon jarring on one's eye or ear, there is much valuable material. The book provides a proper theme for those teachers of medicine who have remained students.

WILLIAM B. BEAN, M.D.

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Second edition. By Lawson Wilkins, M.D. Price, $17.50. Pp. 527, with 168 figures and 35 tables. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This is a revised edition of a book which has proved itself an excellent clinical reference source during the past seven years. The book is written for the clinician, and each subject is approached from the standpoint of the clinician faced with the differential diagnosis of a congenital anomaly or an endocrine disorder which may be helped by treatment.

New chapters discuss the chemistry and physiology of the thyroid and adrenal hormones. The therapeutic use of cortisone in the adrenogenital syndrome stems from the author's pioneer work in this syndrome, which established its basic etiology. The author shows his acumen in withholding judgment of the clinical significance of the chromatin test in various genital malformations. He suggests that the term "intersex" be reserved for those cases which are not due to adrenal disorders.

A chapter entitled "Diagnostic Methods: Hormones, Assays and Tests" explains chemical nomenclature, discusses the general principles of fractionation and measurement of steroids, and points out the diagnostic applications and limitations of these methods. This is a valuable reference book for every internist, pediatrician, gynecologist, and urologist.

JAMES T. BRADBURY, Sc.D.

History of Hydraulics. By Hunter Rouse and Simon Ince. Price, $5. Pp. 269, with profuse illustrations. Iowa Institute of Hydraulic Research, Iowa City, 1957.

The history of medicine may be looked upon as an important element of the history of the times and the ideas of any given age and place. To a surprising degree this is true of the history of many professions. While one would hardly suppose that hydraulics as such had very much to do with medicine, this is far from being an accurate view. There are numerous connections. The importance of hydraulics to physiology, particularly the physiology of the circulation, is revealed again and again to anyone who reads this fascinating history of hydraulics by Rouse and Ince. If one happens to believe that history is useful today, showing us that our problems are not unique and how other peoples and other times have faced theirs and tried to settle them, this book will have interest. History necessarily looks largely at the recent past and dimly at the distant past. This reciprocal influence of time on history may go to the extreme of having the present occupy the entire field of attention and with no time for the past.

In many respects the history of hydraulics has striking parallels with the history of medicine. There is a vast unknown of a forgotten antiquity when the forces of gravity were observed, and empirical observations about pressure, volume, and flows must have been worked out at least to a crude rule of thumb. In historic times in the engineering feats of the Egyptians, the theoretical constructs of the Greeks, and the practical waterworks of the Romans we see over and over again empirical observations leading to experiments which then had practical applications. Speculation and philosophy may be a byproduct of this cycle or may stimulate or thwart its progress. The middle ages contributed little. Even the Renaissance, with its reawakening of humanism and its contact with observations made by the Greeks, did not lead to very effective experimental works. Only with the rise of mathematics and mechanics, which developed rapidly in the post-Renaissance period, do we find hydraulics achieving the rank of a science. This science, to be sure, is not above making effective use of empiricism, which it needs for the surprisingly large number of unsolved problems which remain despite magnificent accomplishments. We rarely consider the fact that a special form of hydraulics has contributed largely to the progress of aeronautics. The contributions of hydrodynamics to hemodynamics are equally conspicuous. To those who relish the attribution of originality or discovery to the true discoverer, it will be of more than passing interest that tests of flow in tubes, pipes, and capillary channels, which led to a formulation we refer to as Poiseuille's law, was done first by the German hydraulic engineer Hagen. Appropriate references are made to Hagen's work and included in this history also are his pioneering efforts, later and independently repeated by Poiseuille. I find pleasure in realizing that Benjamin Franklin, that omnivorous natural historian and natural philosopher, designed towing tanks to test the shape and resistance of various forms of water craft before anybody else had done or reported similar tests.

This history, the first of its kind in the field of hydraulics, while it has importance for those interested in history and in medical history, also is a book which should be known to all

physicians interested in the dynamics of flow in tubes and the hydraulic principles which govern many of the transactions which take place in what Robert Hooke was pleased to call "the several offices and shops of a man's body."

WILLIAM B. BEAN, M.D.

Laboratory Applications in Clinical Pediatrics. By Irving J. Wolman, M.D. Price, $15. Pp. 1019. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

Although most of the information is readily available in standard textbooks of pediatrics, the pediatrician and general practitioner may find the book by Wolman a convenient source of reference in the interpretation of laboratory tests. Discussions of the indications for performing various studies and of frequent errors in interpretation provide the major contribution. The general outlines for performance of the various tests will aid in evaluation of results obtained but in most cases are not sufficiently detailed to permit establishing the method in a laboratory.

No mention is made of the rapidly expanding field of laboratory investigations of congenital heart disease. With this exception, nearly every test commonly employed in pediatrics is discussed. Studies of the hematopoietic system are considered in a particularly comprehensive manner (340 pages). Other sections include infectious diseases and chemotherapy (195 pages), organic and inorganic constituents of the blood (152 pages), cerebrospinal fluid (93 pages), liver and gastrointestinal tract (93 pages), and urine and kidneys (80 pages).

Because individual statements in the text are not documented, the reader is often unable to determine whether a statement represents the opinion of the author or is based on information appearing in one of the references listed at the end of the chapter. Similarly, the origin of data included in the tables of normal values is frequently not clear. The excellent and comprehensive lists of references, mostly recent, contribute greatly to the potential usefulness of the book.

SAMUEL J. FOMON, M.D.

Modern Ideas on Spontaneous Generation. Conference Chairman, Ross F. Nigrelli. Published in *Annals of the New York Academy of Sciences*, Vol. 69, pp. 255-376. Price, $2.50. Pp. 120. New York Academy of Sciences, 2 E. 63d St., New York 21, 1957.

Man has always been a probing, exploring creature, whether it be as a traveler or a visitor of strange new lands or in the realm of ideas. Perhaps that is what made him man. A puzzle second only to the one which deals with the significance and mechanism of life itself concerns the origin of life as we know it. Man looks backward into antiquity to find origins. When this antiquity is measured by millions of years, he immediately confronts the need of full extrapolation. What he can judge as he studies the properties of life today must be used to test the circumstances under which life may have arisen on earth. This symposium deals with the beginnings of life and not the now defunct heresy of spontaneous generation occurring continually. Since the days of Spallanzani and Pasteur, no sensible man has believed that repeated acts of spontaneous generation occur with the formation of complex organisms.

Today no one seriously doubts that all life comes now from preexisting life. Still, our growing concept of evolution and increasing knowledge of biochemistry require an acceptance that life emerged from nonliving materials in the past. This remarkable conference deals with an interdisciplinary approach to a number of problems concerned with such questions.

Among many requisites upon which is based any philosophy of evolution there must be a system of precise replication, the possibility of mutation and sexual reproduction allowing for an almost infinite profusion of combinations of genetic factors. Much of the discussion in the symposium deals with the chemical compounds which are present universally in living matter, proteins, nucleic acids, and compounds which have to do with the transfer of energy-rich phosphate groups, of which adenosine triphosphate is the most prominent. Each of these compounds is concerned, among other things, with replication, which requires energy, the control of energy by kinetic and catalytic modulation, and spatial arrangements, which govern the precise pattern which gives species stability within ranges limited only by mutations. Even for the physician who is not trained in advanced chemistry or the biophysics of the cell, the essays in this symposium provide insights and stimulating thoughts about how organic compounds might have been formed in the early primitive earth, the relation of electrolytes to the mechanisms by which nuclear material and genetic control may be exerted, high-energy phosphorus and the origin of life, the early beginnings of photosynthesis, the origin of optical

activity, the gene in evolution, and various studies of protein structure and function. Taken in its broad sense, this book should appeal to anyone interested in life from the medical and scientific point of view, especially human life and its vicissitudes as well as its proper function.

WILLIAM B. BEAN, M.D.

The Changing Patient-Doctor Relationship. By Martin G. Vorhaus, M.D. Price, $3.95. Pp. 310, with illustrations. Horizon Press, Inc., 220 W. 42d St., New York 36, 1957.

Feeling as I do that communication via the written word is deteriorating in medicine and that we frequently have the deterioration before our eyes in undergraduate medical students, I see some of the reasons for the criticism that the modern physician is unable or unwilling to communicate with patients and their relatives in ordinary terms which they can understand. They sense that he is aloof. Sometimes he is aloof. Part of this, no doubt, results from the attitude of his teachers. Part comes from the natural difficulty of communicating ideas.

The upshot is a considerable clamor against doctors in the lay press, in letters to the editor, and as one meets people. In everyday discussions, our friends are more than willing to issue complaints. Laymen who read Dr. Vorhaus' book on "The Changing Patient-Doctor Relationship" would gain insights to dispel some of their preconceptions and misconceptions. While a detailed study of the case reports might suggest that doctors have both more wisdom and more success than many actually do, the importance of the physician as a stabilizing and pathfinding influence for patients is well illustrated in the series of case reports which are so realistic as to belie the caveat in the front of the book that "no actual person is described in any of the case histories in this book." If these are indeed fictional, they must be based on extensive experience. Many of them are almost like excerpts from tape recordings with a certain amount of editing and polish. The author accepts the Freudian tenet that recognition of unseen or repressed forces of an emotional kind will resolve the neuroses which are said to result from such hidden or repressed forces. Of course this is not explicitly stated, nor is it explicitly demonstrated in this book. I suspect that much of the good which occurs comes from the sympathetic and responsive attention of the physician as "your most enchanted listener." Regardless of what explanation one accepts, in the social transaction between patient and doctor, a physician must give the patient his whole and undivided attention. Cure then may follow care, for this excellent book illustrates and embodies the truth of those good and wise words of Peabody that "the secret of the care of the patient is in caring for the patient."

WILLIAM B. BEAN, M.D.

Medical Support of the Army Air Forces in World War II. By Mae Mills Link and Hubert A. Coleman. Price, $7. Pp. 1027, with 52 figures, 19 charts, and 97 tables. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., 1955.

This extremely accurate and detailed book does what its authors intended of it—it fills "a gap in the medical history of that period."

After a concise summary of "Aviation Medicine" from the establishment of the Aeronautical Division of the Army, in 1907, to the onset of World War II, efforts of the few flight surgeons then trained are set forth, and their tribulations, stymies, and achievements are aired.

Few were in a position to survey that world-wide scene of medical activities. We knew details of our niche and little of the problems of those ten thousand miles away or at a nearby air base.

Individual theaters of war are considered in turn, and the medical support problems, detailed. Ingenuity almost beyond human capability was displayed everywhere.

Air evacuation; paramedic activities; air-sea rescue; pressurized cockpits; demand oxygen systems; escape procedure; ditching procedure; arctic, jungle, and desert survival; definitive treatment at or close to the "front"; protective armor, and early rehabilitation were invented or first put to practical use. Many of us had our baptism in epidemics of infectious hepatitis, malaria, and bacillary and amebic dysentery.

Accounts of professional responsibility without medical facilities thread their way through the theaters of war in the chapters of this book. The corrected version of Air Force Medical Service today had its roots in the obvious shortcomings of a decade and a half ago.

As a historic reference, this work is admirably done. It was ten years in the doing. Its flawless recounts will provoke delightful nostalgia in some. It reads as nearly like a novel as an account of a restricted facet of a global war can possibly read.

LIEUT. COL. PHILIP G. KEIL, (MC), U. S. A. F.

Gastrointestinal Obstruction. By Meyer O. Cantor, M.D., M.S., F.A.C.S. and Roland P. Reynolds, M.D., F.A.C.S. Price, $18. Pp. 565, with 415 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

"Gastrointestinal Obstruction" is an encyclopedic review of the present status of this clinical problem. The first chapter is a brief presentation in chronological fashion of most of the significant contributions upon which current concepts stand. A succinct outline of the important embryology, a discussion of the pertinent anatomy, and an excellent discussion of gastrointestinal physiology as related to intestinal obstruction follow. The signs and symptoms of intestinal obstruction as they occur at all levels of the gastrointestinal tract, starting with the esophagus and ending with the anus, are methodically and comprehensively presented. Considerations peculiar to intestinal obstruction as it occurs during pregnancy, in children, and in the elderly are enumerated in separate chapters, which are well illustrated with drawings, case histories, and appropriate pictures of radiograms. The indications for and technique and interpretation of appropriate radiologic examinations are well stated and illustrated by radiographs and case histories. A plausible discussion of the pathogenesis of distention occurring with mechanical obstruction and paralytic ileus precedes the excellent detailed chapter on gastrointestinal intubation. The indications and contraindications for intubation, choice of the proper tube, advantages and disadvantages of available tubes, technique of intubation, place for radiological visualization of the tube, benefit to be expected from intubation, and complications of intubation are exhaustively and lucidly discussed. There is a brief and useful discussion of fluid and electrolyte balance. The topics covered related to operative considerations include anesthesia, the indications and contraindications for primary resection and anastomosis, and evaluation of the divisionary procedures employed in intestinal obstruction. Individual chapters on relevant bacteriological considerations, intestinal obstruction following gastric and colonic surgery, and nonobstructive lesions which may give rise to a clinical picture indistinguishable from mechanical obstruction are included. This volume is concluded with a consideration of the most important factors contributing to the mortality associated with intestinal obstruction.

The text is well documented by a large number of references which are presented in the form of an easily used bibliography. Perhaps the less sophisticated reader would have profited from fewer carefully selected references. Reaching for completeness, the authors have at times failed to provide the reader with clear-cut recommendations concerning which of the several methods of treatment or concepts are better or more acceptable. The practicing surgeon, the main target for this book, will find some sections elementary and tedious. The repetition which occurs will be obvious only to those reading from cover to cover. Most of the recommendations made and concepts expressed are in keeping with current opinion. However, discussions such as that of carcinoma of the esophagus and the use of enterostomy for decompression of the small bowel are not up to date and may mislead the less experienced reader. All surgeons whose practices include patients with intestinal obstruction will find this volume especially interesting and a valuable addition to their personal libraries. This monograph provides a rich source of pertinent information for others interested in either clinical or investigative aspects of intestinal obstruction. The text is so written as to be practical as a reference source for the medical student and as such should be included in all medical libraries. The printing and binding are satisfactory; the price seems reasonable.

J. A. BUCKWALTER, M.D.

Uniqueness of the Individual. By Peter B. Medawar. Price, $4. Pp. 191, with illustrations. Basic Books, Inc., 59 Fourth Ave., New York 3, 1958.

This book is a collection of essays; it consists of a series of brilliant and witty discourses on biology, with the emphasis on man as an important aspect of biology. Peter B. Medawar is the Jodrell Professor of Zoology and Comparative Anatomy of University College, University of London. The essays were given originally as lectures at diverse places and times, but the unifying theme of dynamic biology brings them into a harmonious whole, which develops as though they had been planned as chapters in a book. The essay

on old age and natural death will please those of a philosophic bent as well as gerontologists, for implied in understanding life is understanding death and implied in understanding death is understanding life. These essays have many biological and Darwinian sidelights and implications. Medawar's views are summed up in a sentence: "Senility is an artifact of domestication, discovered and revealed only by the experiment of shielding an animal from its natural predators and the everyday hazards of its existence." In this sense "no form of death is less 'natural' than that which is commonly so-called." As an example of the problem, it appears that in its natural habitat no fish ever dies of old age, apparently growing almost without limit. On the other hand, the destruction of all but a few of the innumerable fish hatched from the bountiful roe emphasizes the need for proper relationship between the number of creatures born and the number which reach maturity. In discussing unsolved problems of biology, the problem of growth is dealt with at length, as well as the problem of senescence. Both should be of interest to pediatricians, as well as to those who study the life span of cells circulating in the blood stream under many conditions. His discourse on the scientific method is delightful and gives him an opportunity to express many wise thoughts with sparkle and wit. "The act performed to test a hypothesis may be called an 'experiment.' It is best to use the term in this simple and clean-cut way, rather than to follow common use in restricting its terms of reference to some sort of active messing about with nature." These and other chapters work up to the final essay, entitled "The Uniqueness of the Individual," which brings the rest together. This is approached for the most part by newer understanding of immune mechanisms and other relationships revealed by transplantation of skin grafts and the phenomena of the chimera. The entire essay, developed logically and thoughtfully, has no discussion of Roger Williams' concept of biochemical individuality, which follows a different line of inquiry but arrives at very much the same point. This is a stimulating and challenging book for anyone who is interested in the broader aspects of life taken as they come, not as we think they should be. Its simplicity, its clarity, and the almost lighthearted sense of gaiety which prevails remind one of the unexpected and delightful turns in "Patterns of Survival," by John Hogden Bradley, another biologist who combined brilliant insights with an elegance of style which makes reading stimulating, instructive, and fun.

WILLIAM B. BEAN, M.D.

Hemophilia and Hemophilioid Diseases. By Kenneth M. Brinkhous, B.A., M.D. Price, $7.50. Pp. 265, with 43 tables and 78 figures. The University of North Carolina Press, Chapel Hill, N. C., 1957.

Recorded in this book are the proceedings of an international symposium, "Hemophilia and the Hemophilioid Diseases," sponsored by the National Hemophilia Foundation and held at the Ambassador Hotel, New York, Aug. 24-25, 1956. The volume was intended to "provide a kaleidoscopic view of current ideas of the broad field of hemophilia"; its purpose has been fulfilled admirably. The Medical Advisory Council of the Foundation is to be congratulated for its choice of timely, germaine, and provocative topics as well as for its choice of specialists to discuss them. The geographic and scientific representation is impressive and contributes in large part to the luster and authority of the symposium.

The contents are arranged in a logical manner. First, there are informative papers and discussions on the current status of purification, chemical and physical characterization, isolation, standardization, and assay procedures of antihemophilic globulin (factor). These are followed by reports on inhibitors, anticoagulants, and refractiveness in hemophilia—an exceedingly complex subject but one of great practical significance. The role of platelets in hemophilia follows. The section on the hemophilioid states, including those associated with deficiencies of proaccelerin, proconvertin, plasma thromboplastin component, plasma thromboplastin antecedent, and Hageman factor, is well presented and emphasizes clinical as well as technical and laboratory aspects. An exceptionally fine report on genetic problems and the impact of the genetic approach in the evaluation of cases and laboratory data are especially valuable and emphasize an area too often ignored in the study of coagulation disorders. The diagnosis and medical, surgical, and dental management of hemophilia and related diseases, followed by pathological, clinical, and therapeutic considerations of bone and joint complications, are other significant contributions which add greatly to the survey approach. Lastly, psychiatric and socioeconomic aspects of hemophilia, so important to the patient himself, are discussed.

Many of the data are necessarily highly technical and, to be thoroughly comprehended, require considerable background knowledge of coagulation mechanisms. As with any discipline, this can be acquired with study; the excuse of confusing terminology wears a bit thin. Furthermore, in this volume a glossary with synonyms and symbols is provided. The clinical material is succinct and pertinent, and the individual case histories, exemplitive. The subjects discussed are well documented and supported by the liberal use of graphs, charts, and photographs.

The volume can be recommended highly both to investigators working in this complex area and to clinicians who are called upon to treat disorders of coagulation.

JOHN R. CARTER, M.D.

Cortisone Therapy. By J. H. Glyn, M.A., M.D., M.R.C.P., D. Phys. Med. Price, $10. Pp. 162, with 4 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

In this miniature volume Dr. Glyn has successfully presented the true facts about therapy with the cortisone group of steroid drugs. As with so many forms of treatment, cortisone was welcomed with wild enthusiasm by the medical profession, but in the face of severe and sometimes fatal side-reactions, this enthusiasm was replaced by an alarming degree of skepticism. It is to be imagined that this group of drugs will now assume its proper role in the armamentarium of practicing physicians.

Dr. Glyn has done much to evaluate objectively the place of steroids in the field of medical therapeutics. From his excellent historical review and his easily read description of the chemical and pharmacologic properties of these drugs, one is pleasantly led to the practical problems of cortisone therapy and the more specialized applications of its many similar compounds. Throughout the book he has demonstrated not only a thorough knowledge of his subject but a considerable wisdom in evaluating the effects of this form of treatment.

He wisely states that the brilliant discovery of cortisone by Phillip Hench served more to stimulate interest in the field of rheumatic diseases than to provide effective therapy. His surmise that cortisone and its derivatives may be "all but forgotten" in the next fifty years is probably correct. Nevertheless, its impact has been more than considerable.

Three appendices are furnished which provide lucid descriptions of the technique of intra-articular injection, the methods for evaluating the condition of a patient with joint disease and the results of therapy, and an excellent list of selected books and articles for those who desire more information on this subject.

In spite of the rather high price ($10) for this little book, I feel that it provides a bargain to all who use the adrenocortical steroids in clinical practice.

ROBERT E. HODGES, M.D.

The Electrocardiogram. By Louis H. Sigler, M.D., F.A.C.P., F.C.C.P., F.A.C.C. Price, $8.75. Pp. 312, with 195 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1957.

"The Electrocardiogram" is a concise well-balanced text covering all of the major aspects of electrocardiography. It is written in a clear and lucid style and is presented in an attractive format. This textbook should be of value primarily to the student or to the physician who is interested in obtaining a good fundamental understanding of the problems in electrocardiography. It is a practical book but cannot be considered as a reference for the advanced electrocardiographer. The book is well illustrated, and the quality of reproduction is very good. The book can be recommended as a basic text.

E. O. THEILEN, M.D.

Your World and Mine. Second edition. By Halbert L. Dunn, M.D., Ph.D. Price, $3. Pp. 94. Exposition Press, Inc., 386 Fourth Ave., New York 16, 1956.

A heartbreaking frustration of human existence is the fact that one's accumulated experience and wisdom cannot be transmitted except precariously and in small driblets. This leads the thoughtful person to all manner of apprehension and alarm. Halbert Dunn's essay on human relations, "Your World and Mine," represents an effort to set down on paper the extensive experience in the personal relationships of a man who has achieved a high rank in the field of hospital administration and medical statistics. He sets forth his notion of a constructive philosophy of social organization for modern man based on

man's potential for creative genius as well as the small matters of adjusting to day-by-day existence. Few, I think, would argue with his thesis; but it is far from clear how he would go about making his program an operational one; as the jargon goes, how would he utilize personnel to implement his recommendations? While there is some flavor of Couéism and even the Chamber of Commerce, this results from optimism and not naïveté. Dunn has an enthusiastic and fresh approach which despite the fact that it lacks much as a blueprint makes cheerful reading. If followed it would certainly reduce some of the present-day confusion in the world.

WILLIAM B. BEAN, M.D.

Cardio-Charting: Universal Method of Recording Heart Auscultation. By Arthur Briskier, M.D. Price, $6. Pp. 58, with 12 illustrations. The Macmillan Company, 60 Fifth Ave., New York 11, 1957.

The chief purpose of this fifty-eight-page manual is to describe a method of presenting cardiac auscultatory findings in graphic form rather than in descriptive language in a patient's written record. Symbols are used to denote pitch and intensity of heart sounds as well as pertinent information about murmurs. The author suggests that this method of charting heart sounds and murmurs will simplify difficulties in communication and perhaps increase the accuracy of the recorded findings. No doubt Dr. Briskier's method will be of some value to the physician interested in becoming adept at this form of shorthand, using either Dr. Briskier's symbols or some of his own devising. It would be convenient for serial examinations of the same patient by the same physician. One rather minor advantage of the graphic method is that it conserves space on the written page. However, inasmuch as auscultation is subjective, I doubt that recording the findings in graphic form will be more accurate than a carefully written description when one physician compares his findings with another's. In my opinion graphic recording such as this is not likely to find wide acceptance.

E. O. THEILEN, M.D.

Urine and Urinary Sediment, a Practical Manual and Atlas. Second edition. By Richard W. Lippman, B.S., M.D. Price, $8.50. Pp. 140, with 92 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The second edition of this monograph on the examination of the urine has been enlarged to include thirty-six more colored photographs of urinary sediment. The text has been revised to include a few more topics and has been brought up to date. The bibliography has been expanded from 93 references in the first edition to 232 in the second.

For those unfamiliar with the first edition of this book, it should be pointed out that this unique volume is noted for its fine color photomicrographs of the urinary sediment and its practical, pithy, and wise discussion of the urine examination. Details of most simple laboratory examinations of the urine are given. The second edition is a worthy offspring of the first. The photographs are generally of excellent quality, clear, and informative, although a few new ones appear to be unnecessary. The text continues to be well organized, understandable, and full of important observations.

It was my pleasure to introduce the first edition of this book to several classes of medical students. I found it a valuable aid in demonstrating the characteristics of abnormal urinary sediment and in pointing out the significance of the formed elements in the urine. Laboratory technicians also have found this book of great practical value. The second edition should continue to serve well these and other students of the urine. However, chiefly because of the nature of the subject, the additions found in the second edition do not render the first edition obsolete, and I would not buy a second edition volume if I had a copy of the first.

In the foreword of this monograph the author states that Dr. Thomas Addis, with whom he studied, sought ways to "make the information derived from precise observation accessible to the clinician and applicable to the patient." This book does this in an unpretentious and extremely effective manner.

WALTER M. KIRKENDALL, M.D.

News and Comment

ANNOUNCEMENTS

Residency and Research Fellowship in Cardiology.—A residency and a research fellowship in cardiology are being offered at the City of Hope Medical Center in Duarte, Calif. The residency will emphasize clinical aspects of diagnosis and treatment of heart disease and cardiac catheterization. The research fellowship will provide more detailed training in techniques of physiologic investigation of patients with cardiovascular disorders and also an opportunity for the fellow to devote approximately one-half his time to a research project in the animal or clinical laboratories. Candidates must be graduates of approved medical schools and, except in unusual instances, must have completed at least one year of residency training in internal medicine for the residency and two years for the fellowship. The residency is for a period of one year, with salary stipend of $3600. The fellowship is for a period of one year and may be renewed for one additional year, with salary stipend of $4000 to $4800. Facilities are available for housing and maintenance on the grounds, and these facilities can accommodate wives but not children. Correspondence should be addressed to Max Harry Weil, M.D., Ph.D., Chief, or Morse J. Shapiro, M.D., Senior Consultant, Section of Cardiology, City of Hope Medical Center, Duarte, Calif.

American Goiter Association Meeting.—The 1958 meeting of the American Goiter Association will be held in the St. Francis Hotel, San Francisco, June 17, 18, and 19, 1958. Hotel Reservations must be secured by writing to Goiter Housing Bureau, Room 300, 61 Grove St., San Francisco, and be accompanied by a deposit of $10 per room.

The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

Secretary of the association is John C. McClintock, M.D.

XVIth International Congress of History of Medicine.—The XVIth International Congress of History of Medicine will take place at the Faculty of Medicine of Montpellier from Monday, Sept. 22, to Sunday, Sept. 28, 1958, under the general presidency of Monsieur le Doyen Giraud, dean of that faculty.

Inscriptions are being registered now by Monsieur le Professeur Turchini, President of the Organization Committee, Faculty of Medicine, Montpellier, Hérault, France.

The following subjects have been selected for attention: (1) connections between the School of Montpellier and the medical institutions of various countries along the centuries, (2) history and expansion of hospital establishments, (3) medical iconography during the seventeenth century, (4) the New World's contribution to therapeutics, and (5) miscellaneous.

Entrance fees are as follows: 6000 francs (french) for nonmembers of the History of Medicine Society, 4000 francs for membership, and 3500 francs for visitors.

The Organization Committee would be grateful to have, at your earliest convenience, the title of the communication you intend to present (10 minutes for each), as well as a short abstract.

Remittances may be made (by check) either to Compagnie Algérienne de Montpellier No. W12-900-3 or to Compte courant Postal Montpellier No. 1178-03 (XVI Congrès International d'Histoire de la Médecine, Faculté de Médecine, Montpellier).

Meeting of Gerontological Society, Inc.—The 11th annual scientific meeting of the Gerontological Society, Inc., will be held at the Bellevue Stratford Hotel, Philadelphia, Nov. 6, 7, and 8, 1958.

Abstracts of papers for the program should be submitted to the program committee for consideration by July 1, 1958. Abstracts should be sent to the subchairmen of the section in which the author(s) elect to give their paper.

The subchairmen are as follows: Clinical Medicine—Dr. Ewald Busse, Duke University Hospital, Durham, N. C.; Biology—Dr. Morris Rockstein, Department of Physiology, New

York University, 550 First Ave., New York 16; Psychology—Dr. Ethel Shanas, National Opinion Research Center, 5711 S. Woodlawn Ave., Chicago, and Sociology—Dr. W. M. Beattie Jr., Department of Sociology, Washington University, St. Louis.

Exact details as to the length of a presentation and its place on the program will be made available by the appropriate subchairmen. Scientific and commercial exhibits are scheduled with a series of social functions and a meeting open to the public. Chairman of the Exhibitions Committee is Dr. Leo Gitman, 813 Howard Ave., Brooklyn 12.

The plan of the meeting is to serve as a particular source of information in each section in addition to general sessions for the comprehensive information of all students of gerontology.

The co-chairmen are as follows: Dr. Warren Andrew, Bowman Gray School of Medicine, Winston-Salem, N. C., and Dr. Joseph T. Freeman, 1530 Locust St., Philadelphia 2.

IF YOU CHANGE ADDRESS

Please notify us at least six weeks before you make the change.

With your notification, include the address label clipped from the latest copy of the journal. If your city has postal zone numbers, be sure to include the zone number in your new address.

You will want to get your copies promptly; so notify us at least six weeks in advance. Send your change notice to

A. M. A. Archives of Internal Medicine
American Medical Association
535 North Dearborn St.
Chicago 10, Illinois

HYDRATES STIMULATES

Metamucil® does **BOTH!**

In constipation, Metamucil produces soft, easy stools and stimulates gentle peristalsis. Metamucil HYDRATES fecal matter by adsorbing and retaining water within the stool. In this way it prevents hard feces from forming, and it adds to the intestinal residue a soft, plastic bulk which STIMULATES the normal reflex activity of peristalsis.

Metamucil is a brand of psyllium hydrophilic mucilloid with dextrose.

SEARLE

NOW...

advanced treatment for gastri

NEW...

SUSPENSION

ALUDR

Aluminum Hydroxide Gel with Magnesium Hydroxid

with an important NEW *anticholinergic*

AMBUTONIUM

—a highly effective agent exhibiting marked antisecretory activity

for . . . peptic ulcer
hypertrophic gastritis
esophagitis

SUPPLIED: SUSPENSION, bottles of 12 fl. oz. TABLETS, bottles of 100. Each teaspoonful (5 cc.) and tablet contains 2.5 mg. of ambutonium bromide and 8 mg. of butabarbital in combination with aluminum hydroxide and magnesium hydroxide approximately equivalent to 1 teaspoonful of aluminum hydroxide gel and ¼ teaspoonful of milk of magnesia. Also available: Tablets Ambutonium Bromide, 10 mg., bottles of 100.

Wyeth®
Philadelphia 1, Pa.

hyperacidity and hypermotility

TABLETS

OX® SA

...butonium Bromide, and Butabarbital, Wyeth

BROMIDE

with all these combined advantages

for fullest patient care . . .

NEW

anticholinergic Ambutonium bromide, a new potent anticholinergic, has definite antispasmodic effect and significantly reduces gastric acidity, secretory volume, gastrointestinal motility.

sedative Butabarbital, "intermediate" barbiturate, produces sedation within 30 minutes, lasting for 6 to 8 hours—a distinct advantage for the peptic-ulcer patient with accompanying anxiety and tension.

antacid Aluminum hydroxide and magnesium hydroxide for effective antacid, demulcent, and pepsin-inhibiting actions.

anticonstipant Magnesium hydroxide in amount to prevent constipation without undue laxation.

When eliminating the high roughage foods containing irritating bulk—replace them with

L (Levis*) *smooth A (Amplitudo*) *bulk Formula

L. A. FORMULA is a highly refined psyllium type hydrophilic colloid with dextrose and lactose which provides the moist, smooth bulk so essential to normal peristalsis. The smooth bulk of L. A. FORMULA disperses with the intestinal contents to create a soft-formed easily passed stool.

Dosage, details and clinical trial samples are available on request.

Made by BURTON, PARSONS & COMPANY *Since 1932*
Originators of Fine Hydrophilic Colloids
WASHINGTON 9, D. C.

Viokase Pancreatin 4 times the N.F. X minimum potency standards.

VIOKASE

CONFORMS TO PHYSICIANS' COUNCIL INFORMATION ON CHILD HEALTH CODE FOR ADVERTISING

WHOLE PANCREAS
Not an extract!

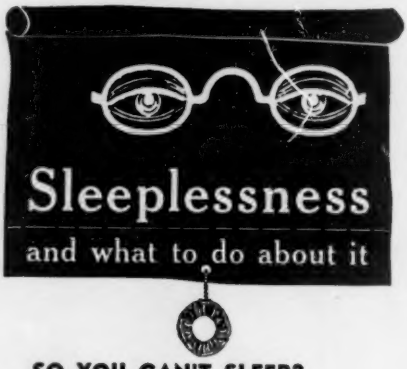
EFFECTIVE substitution therapy in demonstrated pancreatic deficiency.

NOT ENTERIC COATED

Jordan and Grossman; Arch. Surg. 74: 871, 1957
Shingleton, et al; Surgery, 42: 12, 1957
Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956
Krane; Am. Pract. and Digest, 8: 1275, 1957

Literature on request.

VIOBIN, Monticello, Illinois

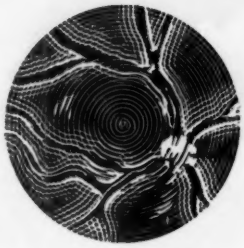


SO YOU CAN'T SLEEP?
by P. H. Fluck
8 pages, 15 cents

SLEEPLESSNESS AND WHAT TO DO ABOUT IT by Donald A. Laird, Ph.D.
8 pages, 15 cents

ROADS TO RELAXATION
by Joseph L. Fetterman, M.D.
4 pages, 10 cents

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois



in severe essential or malignant hypertension

to reduce blood pressure and control symptoms

When 30 patients with hypertensive diseases of varying severity received Methium with Reserpine, 76.6% showed a significant fall in both standing and supine blood pressure. Under treatment for an average of 14 months, nearly all experienced marked symptomatic improvement. Blood pressure reduction was achieved and maintained on " . . . less than half the usual daily requirement of either drug."*

In this combination the ganglionic blocking action of Methium appears to be potentiated by the central vasodepressive effect of reserpine, leading to "...clinically smoother and more satisfactory blood pressure reduction."*

Because lower dosages of each drug are required when used in combination, side effects from Methium with Reserpine occur rarely and are usually mild. Optimal dosage is safely established through gradual increases.

* REFERENCE:
Crawley, C. J. *et al*: N. Y. State J. of Med. 55:*23* (Dec.1) 1955: pp. 3461-3463.

Methium® with **Reserpine**

(brand of hexamethonium chloride)

WARNER-CHILCOTT

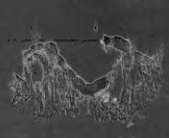
whenever rapid corticosteroid action is imperative

- exceptionally prompt anti-inflammatory, antistress action... effectiveness demonstrable usually within one hour
- 3 to 5 times the milligram potency of hydrocortisone
- virtually no sodium retention, edema, potassium loss

For specific information regarding indications, dosage, side effects, precautions and contraindications refer to Schering literature.

Supply METICORTELONE Soluble Sterile Powder, prednisolone sodium hemisuccinate 50 mg./5 cc.; 5 cc. vial.

Meti—T.M.—brand of corticosteroids.



ANNOUNCING . . . new

METICORTELONE®

prednisolone sodium hemisuccinate

SOLUBLE

for accelerated, accentuated "Meti"steroid effect in adrenocortical failure

associated with emergency or elective surgery or fulminating infections

shock unresponsive to standard therapy
life-threatening drug reactions
sight-threatening posterior-chamber eye lesions

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

(MED. JRL.)—MLJ-316

9 SPECIALTY JOURNALS

PUBLISHED MONTHLY

BY THE AMERICAN MEDICAL ASSOCIATION

NEUROLOGY AND PSYCHIATRY

DISEASES OF CHILDREN

INTERNAL MEDICINE

INDUSTRIAL HEALTH

OTOLARYNGOLOGY

OPHTHALMOLOGY

DERMATOLOGY

PATHOLOGY

SURGERY

each journal offers
the latest medical findings by
outstanding authorities in
its special field . . .
of value not only
to the specialist but
to the general practitioner as well

to order your subscription to one of the A.M.A.'s
specialty journals use the form below

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn • Chicago 10

Please enter my subscription to the specialty journal checked at right.
Keep my name on your list until I ask you to cancel.

Remittance for ☐ one year ☐ two years is enclosed.

NAME_____

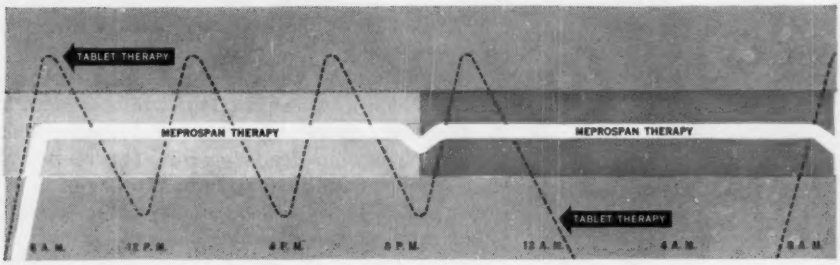
ADDRESS_____

CITY_____ ZONE____ STATE_____

	U.S.A. & Possessions APO's	Canada	Outside U.S.A. & Possessions
☐ A.M.A. Arch. Neurology and Psychiatry	$14.00	$14.50	$15.50
☐ A.M.A. Arch. Dermatology	12.00	12.50	13.50
☐ A.M.A. Arch. Industrial Health	10.00	10.50	11.50
☐ A.M.A. Arch. Internal Medicine	10.00	10.50	11.50
☐ A.M.A. Jrl. Diseases of Children	12.00	12.50	13.50
☐ A.M.A. Arch. Surgery	14.00	14.50	15.50
☐ A.M.A. Arch. Pathology	10.00	10.50	11.50
☐ A.M.A. Arch. Ophthalmology	12.00	12.50	13.50
☐ A.M.A. Arch. Otolaryngology	14.00	14.50	15.50

New... meprobamate prolonged release capsules

Evenly sustain relaxation of mind and muscle 'round the clock



TWO MEPROSPAN CAPSULES IN THE MORNING RELIEVE ANXIETY, TENSION AND SKELETAL MUSCLE SPASM THROUGHOUT THE DAY.

TWO MEPROSPAN CAPSULES AT BEDTIME PROVIDE UNINTERRUPTED SLEEP THROUGHOUT THE NIGHT.

Meprospan*

MEPROBAMATE IN **PROLONGED RELEASE** CAPSULES

- maintains constant level of relaxation
- minimizes the possibility of side effects
- simplifies patient's dosage schedule

Dosage: Two Meprospan capsules q. 12 h.
Supplied: Bottles of 30 capsules.
Each capsule contains:
Meprobamate (Wallace) .....**200 mg.**
2-methyl-2-n-propyl-1,3-propanediol dicarbamate

Literature and samples on request.

WALLACE LABORATORIES, *New Brunswick, N. J.*

*TRADE-MARK CME-6508-48

When "Breakfast Anorexia" must be Overcome

Anorexia upon arising must often be dealt with as part of a therapeutic regimen. In addition to the well-known syndrome of early pregnancy, several other causes of "breakfast anorexia" are recognized. Generally psychological in character, they include fear or lack of enthusiasm in facing the day, distaste or intolerance for the fried and fatty foods commonly served at breakfast, and habit patterns such as late rising with the inevitable morning rush. Obese patients who "cannot" eat breakfast tend to overeat during the day in order to overcome the deficit.

When "breakfast anorexia" must be overcome, physicians find that a dish of steaming oatmeal as the main food at breakfast is a great help in the solution of this problem. Its inviting warmth and delicious taste make the oatmeal dish appealing even when appetite is poorest. It also provides readily available energy for a morning of productive work; it helps to allay hunger throughout the morning; it makes a notable contribution to the day's nutritional needs; it is low in fat, and is easily digested.

Oatmeal is richer in protein than all other whole-grain breakfast cereals. It ranks among the highest in thiamine, and contributes other B vitamins as well. It is outstanding for its iron content.

The correction of "breakfast anorexia" can be made easier in many ways by a morning dish of oatmeal and milk, so quickly and easily prepared, and so gratifying.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

IN DIETARY MANAGEMENT, virtually regardless of the adjustment to be made, oatmeal proves remarkably valuable. It is low in sodium, low in purines, low in inert residue, high in protein, notable for its vitamin and mineral content, yet not excessive in calories.

The Quaker Oats Company
CHICAGO

Now, when you want to restrict the patient's intake of saturated fats you can safely recommend

EMDEE*

margarine

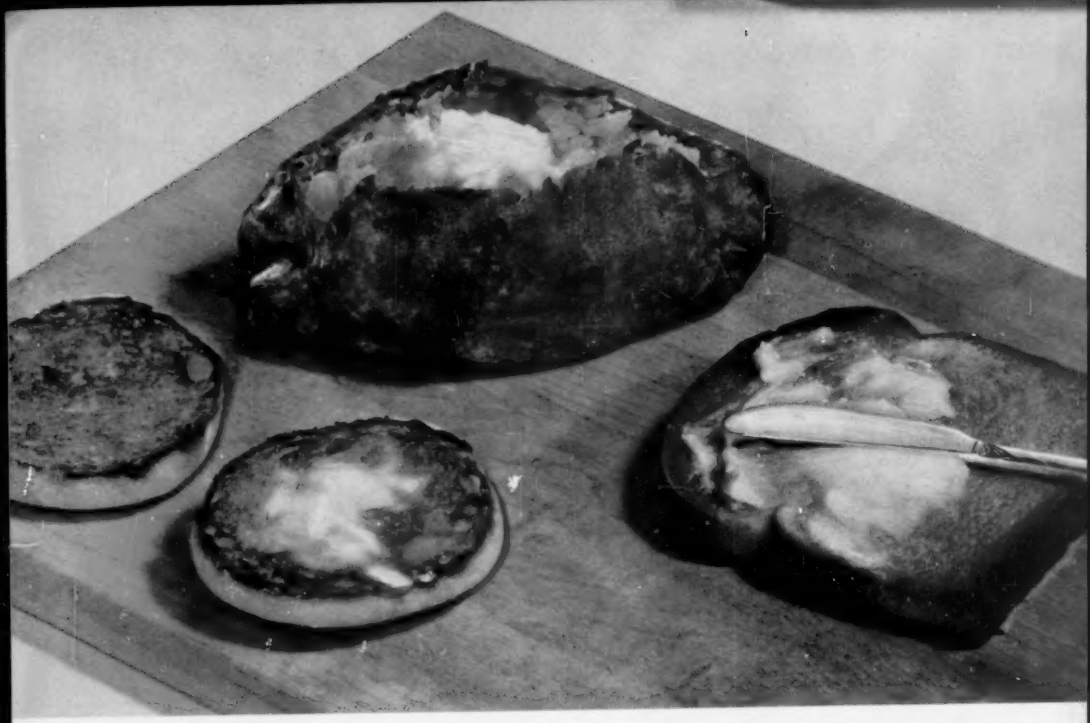
... because its high corn oil content has not been known to elevate blood cholesterol levels

Emdee Margarine is the culmination of several years of research effort by Pitman-Moore Company, directed toward developing a palatable, effective substitute for animal fats and hydrogenated vegetable oils. Because corn oil appears to have merit in controlling serum cholesterol levels it was selected as the basic ingredient in this new and completely different margarine.

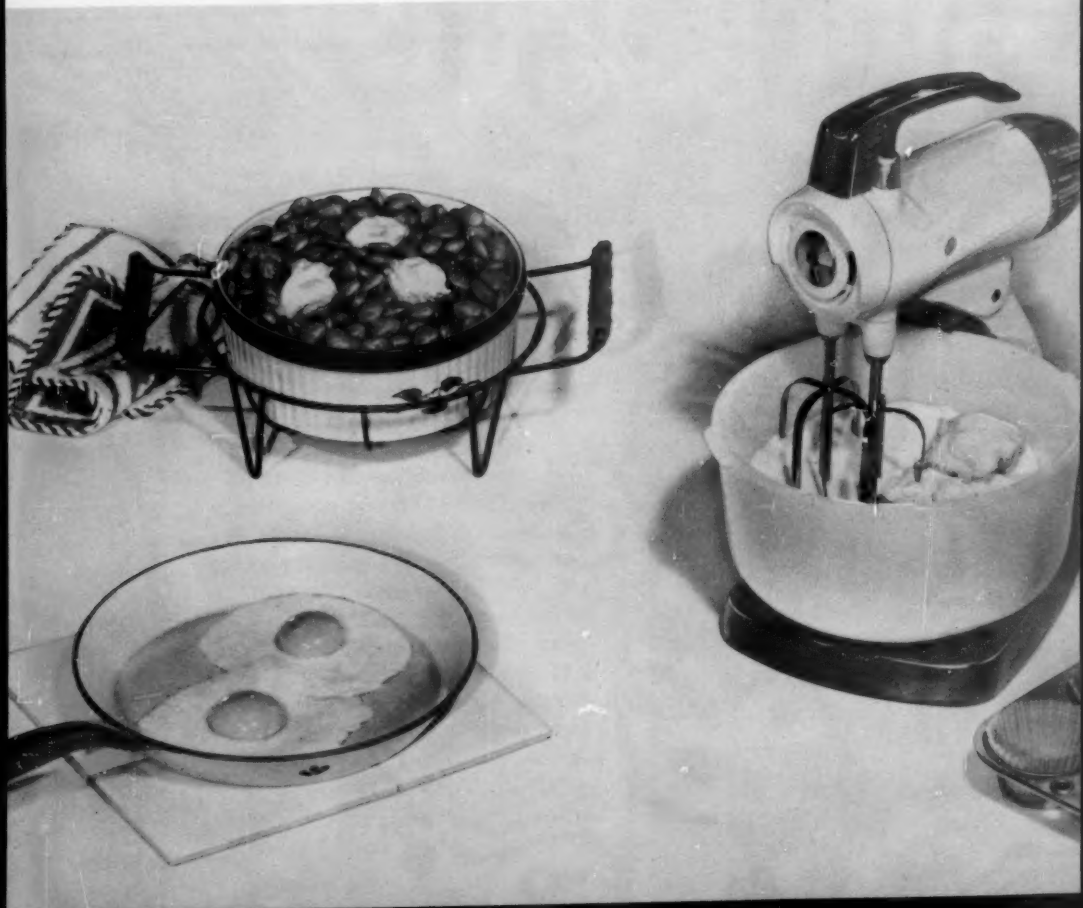
The fine "table spread" texture and appearance of Emdee Margarine is accomplished by special manufacturing processes† which do not alter the natural characteristics of corn oil.

†Patent pending

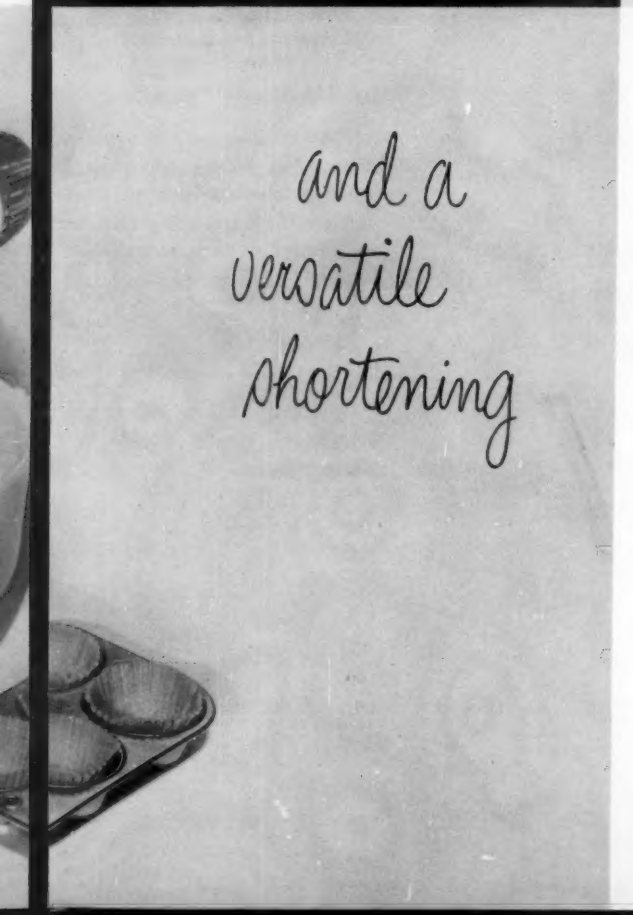
*Trade Mark



THE PRACTICAL ANSWER TO A FRUSTRATING PROBLEM IN DIETARY CONTROL



EMDEE MARGARINE



puts a "safety factor" in the daily diet

Admittedly, the relationship of diet to hypercholesterolemia and atherosclerosis needs further clarification. However, there is ample evidence that with controlled diets the reduction of *saturated* fats and their replacement by *unsaturated* fats can consistently lower serum cholesterol levels. The corn oil in Emdee Margarine is, of course, such an unsaturated fat.

When control of cholesterol levels is desired, Emdee Margarine is a "safe" *replacement* for the customary table and cooking fats that have a high content of saturated fatty acids. The patient is benefited in two ways by routine use of Emdee Margarine as a table spread or kitchen shortening:

(1) The intake of animal fats and hydrogenated oils can be sharply restricted indefinitely . . . without resorting to the so-called "fat free" diets that many patients find almost intolerable.
(2) Daily use of Emdee Margarine, both at the table and in cooking, provides a liberal intake of the *unsaturated* fatty acids believed to be essential in metabolism and important in the control of blood cholesterol levels.

helps assure patient cooperation

The problem of rigid dietary control, so frustrating both to patient and physician, is made easier with Emdee Margarine. Many favorite foods need not be eliminated or restricted, if they are prepared or served with Emdee Margarine. Exceptional cooperation by patients in adhering to this form of diet modification has been reported by clinicians.

a new
"safety factor"
in the daily
diet
OLEOMARGARINE
EMDEE*
MARGARINE
Prepared from corn oil, and hardened coconut oil, pasteurized fat-free milk, salt, lecithin, mono and diglycerides. ARTIFICIALLY COLORED (CAROTENE) and FLAVORED. 15,000 Units Vitamin A and 2,000 Units of Vitamin D added. Two ounces supplies 50% minimum daily requirement of A and D for a child; 47% of A and 8.2% of D for an adult.
Distd. by
PITMAN-MOORE COMPANY
Division of Allied Laboratories, Inc.
Indianapolis, Indiana
Net Weight 1 Lb.
*Trademark

when control

of blood cholesterol

is desired

in EMDEE margarine

80% of the fat content consists of nonhydrogenated corn oil which has been specially processed to preserve its original content of unsaturated fatty acids. Each 100 Gm. of Emdee Margarine provides 34 Gm. of linoleic acid and 18 Gm. of other unsaturated fatty acids. It fully meets identity standards for margarine, including fortification with Vitamin A (15,000 U.S.P. UNITS/LB.) and Vitamin D (2,000 U.S.P. UNITS/LB.)

Caloric content is equivalent to that of any other margarine, 100 calories per tablespoonful.

an "ethical" product

Although Emdee Margarine does not require a prescription, it is distributed *only* to prescription pharmacies and is *not* promoted to your patients through any lay medium.

Supplied: In 1-pound cans. Should be stored in refrigerator or freezer.

PITMAN-MOORE COMPANY
DIVISION OF
ALLIED LABORATORIES, INC.
INDIANAPOLIS 6, INDIANA

just two tablets
at bedtime

for gratifying
rauwolfia response with
virtually no serious side actions

Rauwiloid®
(Alseroxylon)

Riker
LOS ANGELES

in arthritis

'Compazine' reduces the apprehension and anxiety that accompany a long-term and often incapacitating disease. With fears eased, patients often respond better to treatment and in many cases require less specific medication.

'Compazine' Spansule† capsules provide all-day or all-night relief with a single oral dose.

Also available: Tablets, Ampuls, Multiple dose vials, Syrup and Suppositories.

*Compazine**

an agent remarkable for its freedom from drowsiness and depressing effect

*T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

Smith Kline & French Laboratories, Philadelphia